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The American Journal of Medicine

Vol. XV JULY, 1953 No. 1

Editorial

Investigation of the Aging Process . . . . . O. H. ROBERTSON 1

Clinical Studies

Diagnosis of Mitral Regurgitation. An Evaluation of Clinical Criteria, Fluoroscopy, Phonocardiogram, Auricular Esophagogram and Electrokymogram
WALTER H. ABELMANN, LAURENCE B. ELLIS AND DWIGHT E. HARKEN 5

The criteria for diagnosis of mitral regurgitation are in process of undergoing the most searching re-examination because of the necessity for excluding patients with marked mitral insufficiency from valvuloplasty for mitral stenosis. Previously accepted signs, particularly auscultatory, have been found wanting and, indeed, the meticulous analysis of this timely paper, based upon observations at operation in sixty-three patients, would indicate that no one of the several methods of examination is altogether reliable for the purpose. Nevertheless, the authors, after presenting data indicating the relative merits of available methods, conclude that certain combinations of findings are sufficient to warrant or contraindicate surgery in these patients. They conclude that an apical systolic murmur of Grade 2 or less, a left auricle moderately enlarged posteriorly only and showing definite but slight systolic posterior expansion, and evidence of right ventricular enlargement without indication of left ventricular enlargement together give reasonable certainty that no mitral regurgitation is present of a degree sufficient to contraindicate valvuloplasty in patients with the typical findings of mitral stenosis and disability warranting operation.

Early Changes of Mitral Valve Function in Rheumatic Heart Disease. A Clinical, Phonocardiographic and Electrokymographic Study
ALDO A. LUISADA AND GIANO MAGRI 25

Detection of valvular lesions in early rheumatic heart disease and evaluation of their prognostic significance has always been difficult and a stumbling block to clinicians. This study represents an effort to refine diagnosis by combined use of auscultatory, phonocardiographic and electrokymographic technics in fifty-three cases of rheumatic fever. The results, which are of unusual interest, emphasize the uncertainties of ordinary clinical appraisal, particularly in respect to mitral regurgitation, and stress the value of such correlative data obtained at intervals after the acute rheumatic attack.

Quantitative Effects of Medical and Surgical Treatment of Mitral Stenosis on Exercise Tolerance . . . . . ROBERT A. BRUCE AND DAVID L. RODGERS 35

The development of criteria for measuring the degree of severity of mitral stenosis, and the degree of consequent incapacitation, has become more important than ever with the evolution of com-

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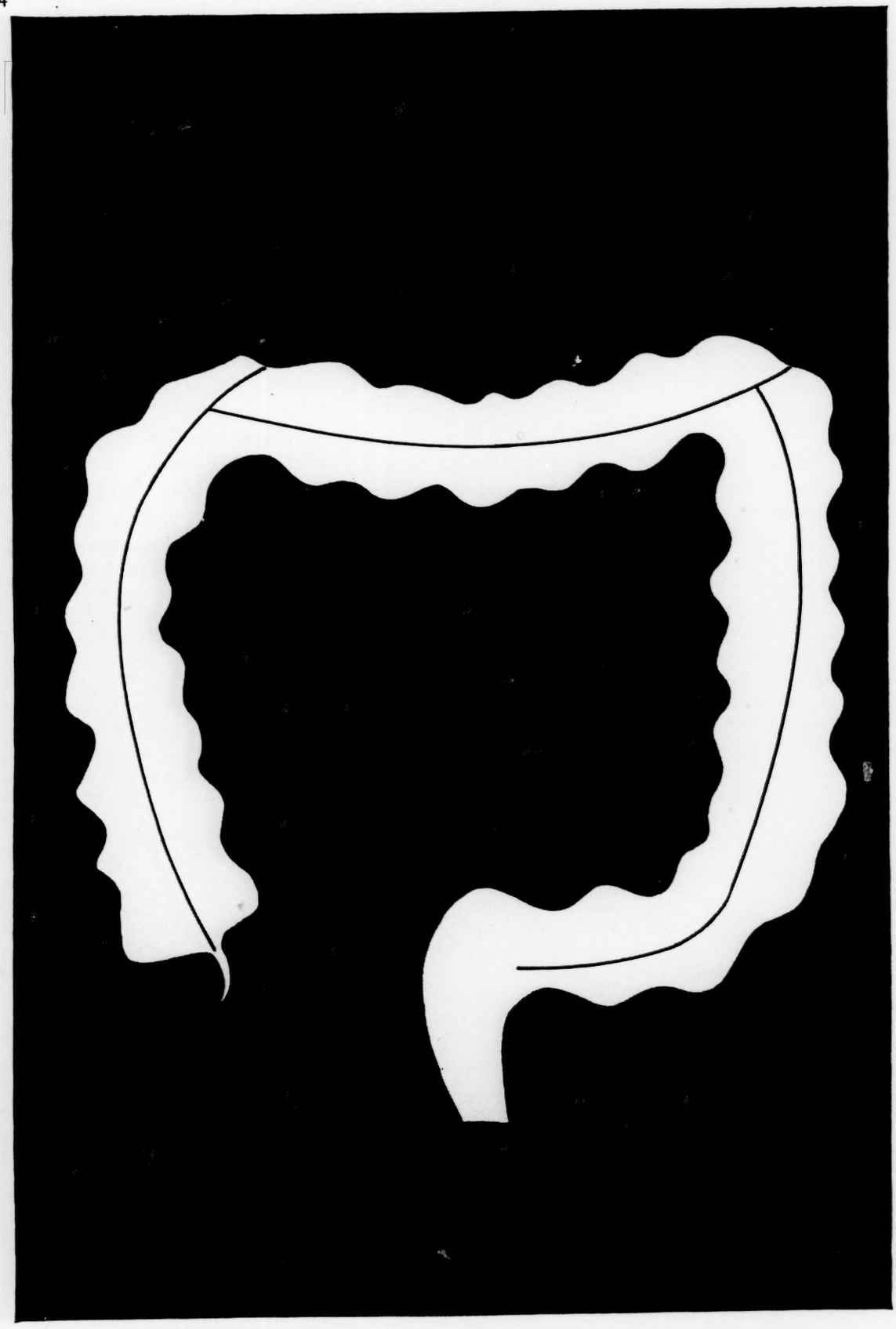

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missurotomy. The authors have devised a standardized exercise tolerance test for this purpose and here report the results of observations in twenty patients before and after medical and surgical treatment. Significant increase in exercise tolerance could be demonstrated in most cases postoperatively but there was subsequent deterioration within three to nine months after operation in some instances. This approach deserves more extensive trial.

Certain Abnormal Circulatory Dynamics of Mitral Stenosis Associated with a Major Degree of Regurgitation . . PETER T. KUO AND TRUMAN G. SCHNABEL, JR. 50

The development of mitral valve surgery has created a need for more precise methods for establishing the presence and degree of mitral regurgitation associated with stenotic lesions. In this report the authors find that a dynamically significant regurgitant stream causes a distinct headward thrust in systole which can be recorded ballistocardiographically as a large, early systolic headward wave appearing just before the J wave. This observation, together with relevant elektrokymographic studies, may prove to be of considerable help in screening patients for mitral valvulotomy.

Ventilatory Studies in Mitral Stenosis. A Comparison with Findings in Primary Pulmonary Disease

N. ROBERT FRANK, DAVID W. CUGELL, EDWARD A. GAENSLER AND LAURENCE B. ELLIS 60

In view of the early clinical manifestations of difficulties in respiration in patients with mitral stenosis, and the later extensive pulmonary involvement, precise measurements of ventilatory functions in such patients are of particular interest. The present study describes the findings in sixty-two cases. At first normal, increasing disabilities and hemodynamic abnormalities are associated with progressive ventilatory defects which do not, however, reach the proportions observed in primary pulmonary disease with obstructive or restrictive ventilatory insufficiency until advanced congestive heart failure develops.

Review

Occlusive Auricular Thrombi

JACQUES B. WALLACH, LESLIE LUKASH AND ALFRED A. ANGRIST 77

The authors summarize sixteen of their own cases of occlusive auricular thrombi (culled from over 8,500 consecutive autopsies) and, on the basis of their findings, critically review current concepts of the relation of such thrombi to the clinical symptomatology. The essential consequence of all these space-occupying masses in the left auricle would seem to be decreased filling of the left auricle and therefore of the left ventricle, with diminution of cardiac output. This, together with a variety

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of other more or less incidental sequelae, would seem to account adequately for the associated clinical phenomena which therefore are not specific or pathognomonic.

Seminars on Neuromuscular Physiology

Muscle and Nerve—Physiologic Orientation . R. W. GERARD AND R. E. TAYLOR 83

By way of introduction to modern concepts of neuromuscular physiology in normal man and in relevant diseases, the authors contribute a general orientation for purposes of perspective. First considered are the motor unit as a whole, and the effects of nerve degeneration. Then the manner and mechanisms of excitation and nerve impulse transmission are described. A description of the myoneural junction follows. The paper concludes with a concise discussion of the physiology of muscle contraction. An extensive bibliography for further reading is appended. The whole makes an authoritative, well balanced, up-to-the-minute introduction to this complex subject.

Combined Staff Clinic

Bone and Metabolic Diseases of Bone 99

Combined Staff Clinics (Columbia University College of Physicians and Surgeons)—This conference begins with a summary of the major known facts about the composition of the bone mineral and how it is laid down. Then follows a discussion of the mechanisms of action of parathyroid hormone, vitamin D and other factors participating in the regulation of calcium and phosphorus metabolism in relation to bone. The conference closes with a consideration of the clinical aspects of generalized osteitis fibrosa, osteoporosis and osteomalacia.

Clinico-pathologic Conference

Bronchial Asthma 112

Clinico-pathologic Conference (Washington University School of Medicine)—This case afforded opportunity for an interesting and informative discussion of bronchial asthma, particularly of the intrinsic type. Among the topics touched upon are the significance of associated eosinophilia, the development of cor pulmonale, the relationship to polyarteritis nodosa and to emphysema and the paucity of findings at necropsy.

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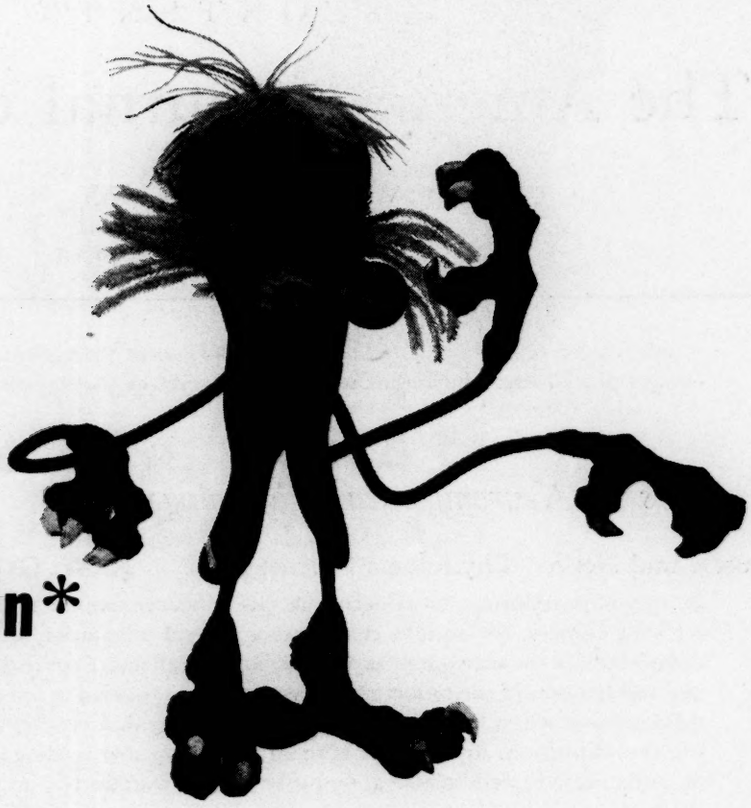

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Case Reports

Renal Hyperchloremic Acidosis. Familial Occurrence of Nephrocalcinosis with Hyperchloremia and Low Serum Bicarbonate
CAPT. GEORGE E. SCHREINER, CAPT. LLOYD H. SMITH, JR. AND LAURENCE H. KYLE 122

Two new cases of renal hyperchloremic acidosis, one with definite familial incidence, are described; the only uncertainty in the diagnosis being the circumstance of large milk ingestion over many years. A sane discussion of possible mechanisms is included in this instructive presentation.

Hand-Schüller-Christian Disease or Eosinophilic Xanthomatous Granuloma
ELIZABETH MEYER 130

Interesting necropsy findings in a case followed clinically for fifteen years, revealing the variable natural course of the disease and the relation to other histiocytoses of bone.

Auricular Sounds in a Case of Auricular Flutter J. PARK BIEHL AND DAVID L. SIMON 134

The precordial clicks sometimes heard in association with auricular flutter at low ventricular rates can be very puzzling, hence the appropriateness of this case report.

Fatal Bone Marrow Embolism Occluding the Pulmonary Arteries
DONALD F. GLEASON AND ARTHUR C. AUFDERHEIDE 137

This is an interesting report of fatal occlusion of the pulmonary arteries by bone marrow emboli, occurring under unusual circumstances. Probably some cases of previously reported fatal fat emboli following fracture really fell in this category.

Advertising Index on 3rd Cover

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1. Rogers, M. P., and Gray, C. L.: *Am. J. Digest. Dis.* 19:180, 1952.

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* *Postgrad. Med. 9:106, 1951.*

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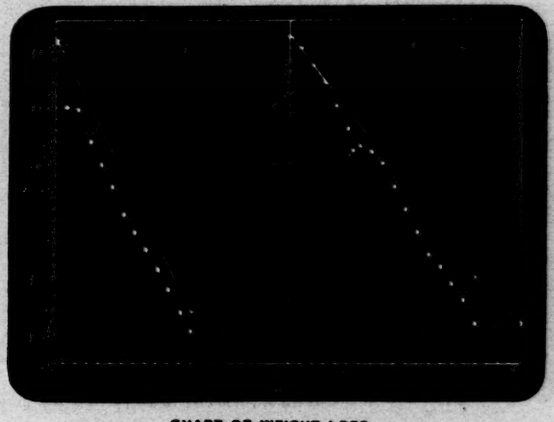

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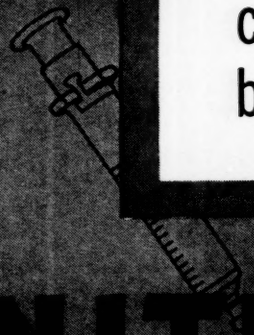

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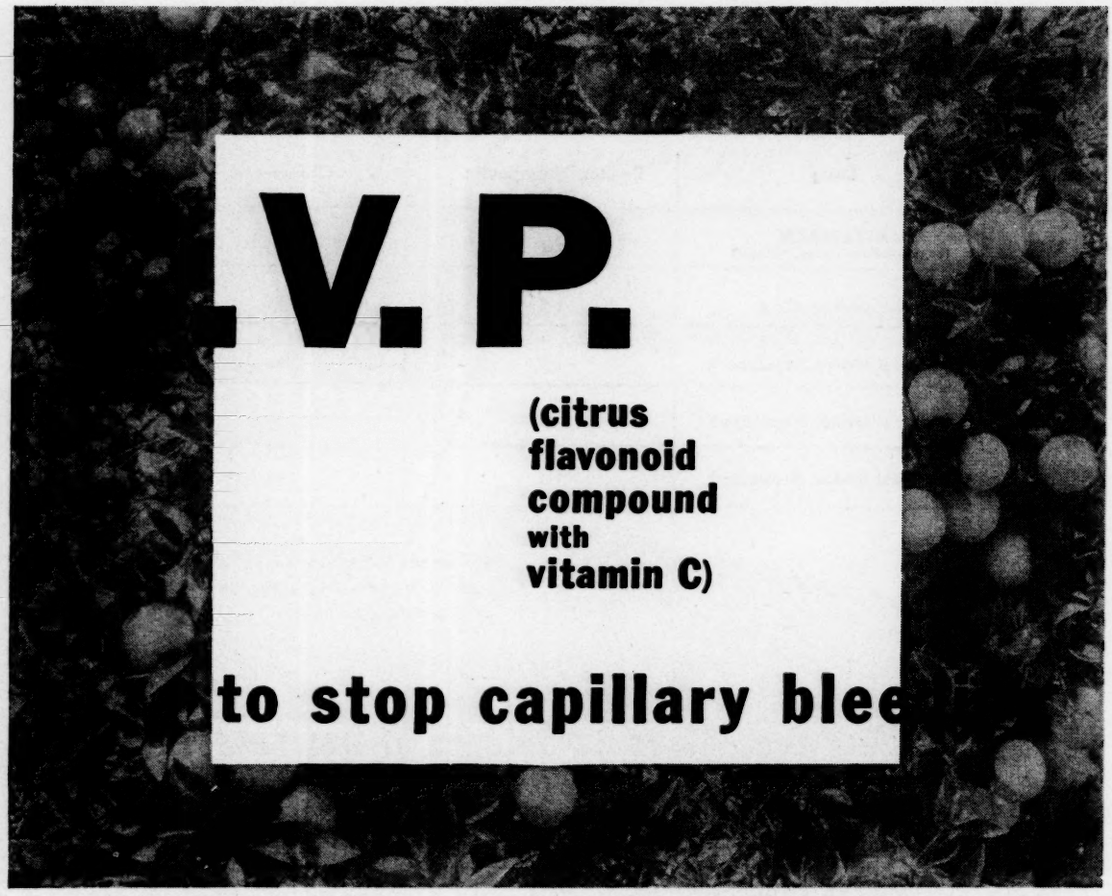

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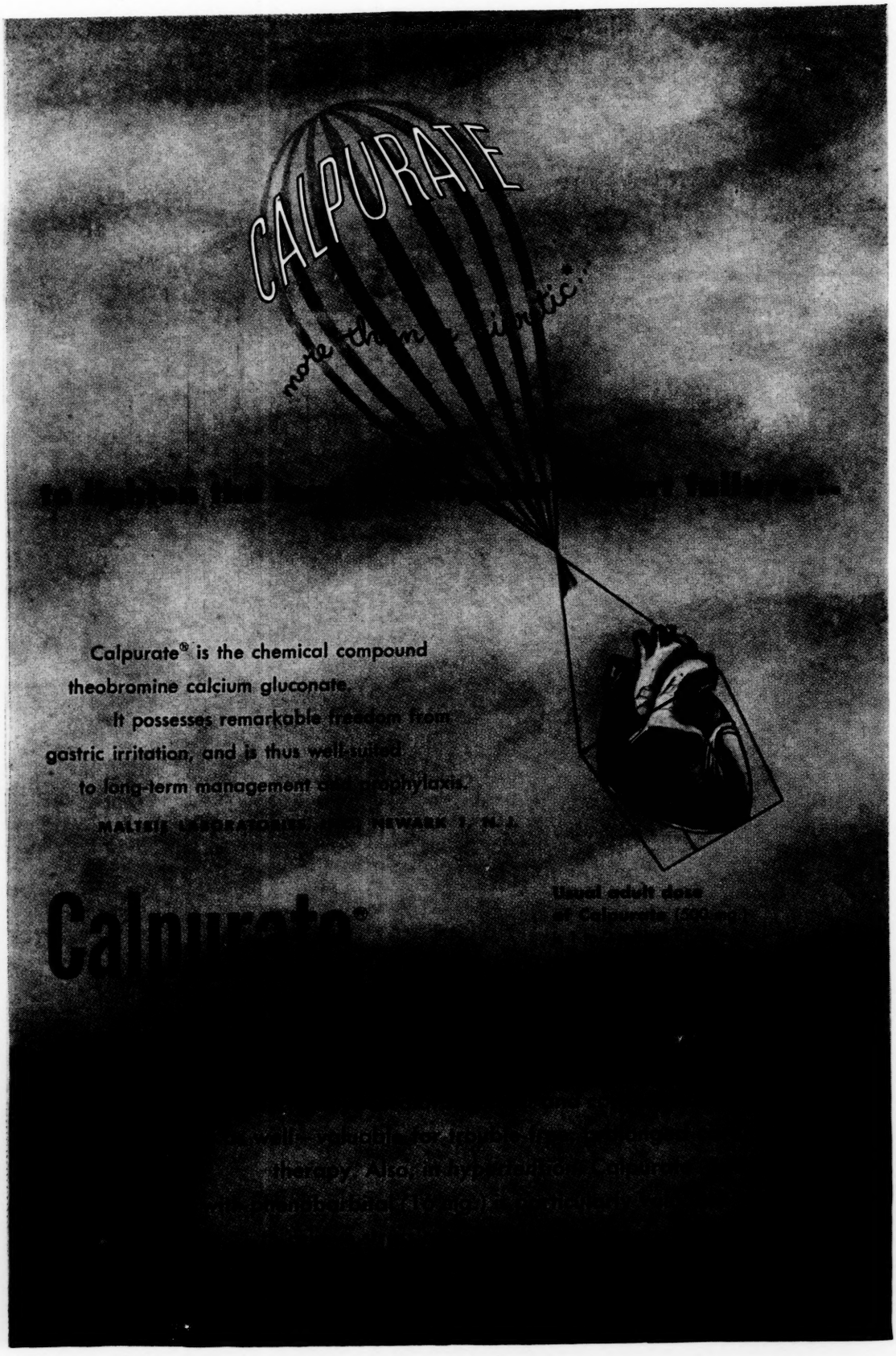
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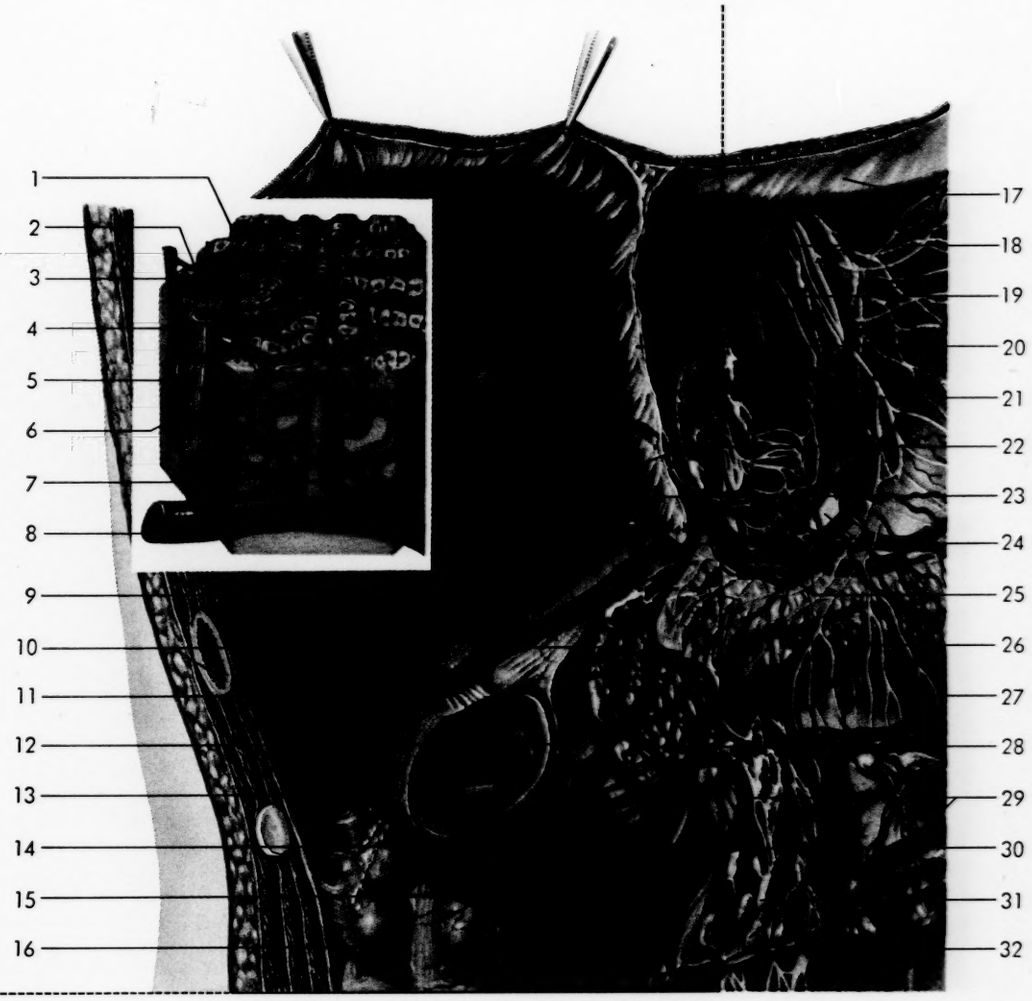

1 Sinusoid
2 Arteriole
3 Bile capillary
4 Branch of hepatic artery
5 Bile duct
6 Branch of portal vein
7 Central vein
8 Branch of inferior vena cava
9 Right lobe of liver
10 Common bile duct and tenth rib
11 Gallbladder
12 Papilla of Vater
13 Transverse colon
14 Duodenum
15 Branches of right colic artery and vein
16 Ascending colon
17 Coronary ligament and esophagus
18 Left hepatic vein and left vagus nerve
19 Inferior vena cava and right vagus nerve
20 Falciform ligament and branch of portal vein
21 Abdominal aorta and celiac plexus
22 Hepatic duct and hepatic artery
23 Cystic duct and celiac artery
24 Celiac ganglion and gastroduodenal artery and vein
25 Left gastric artery and coronary vein
26 Pancreatic duct
27 Right gastroepiploic artery and vein
28 Head of pancreas and pancreaticoduodenal artery and vein
29 Superior mesenteric artery and vein, and jejunum
30 Right colic artery and vein
31 Superior mesenteric lymph nodes
32 Inferior mesenteric vein and left ureter

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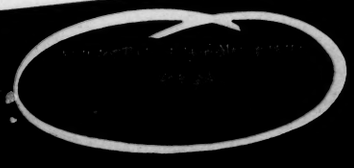

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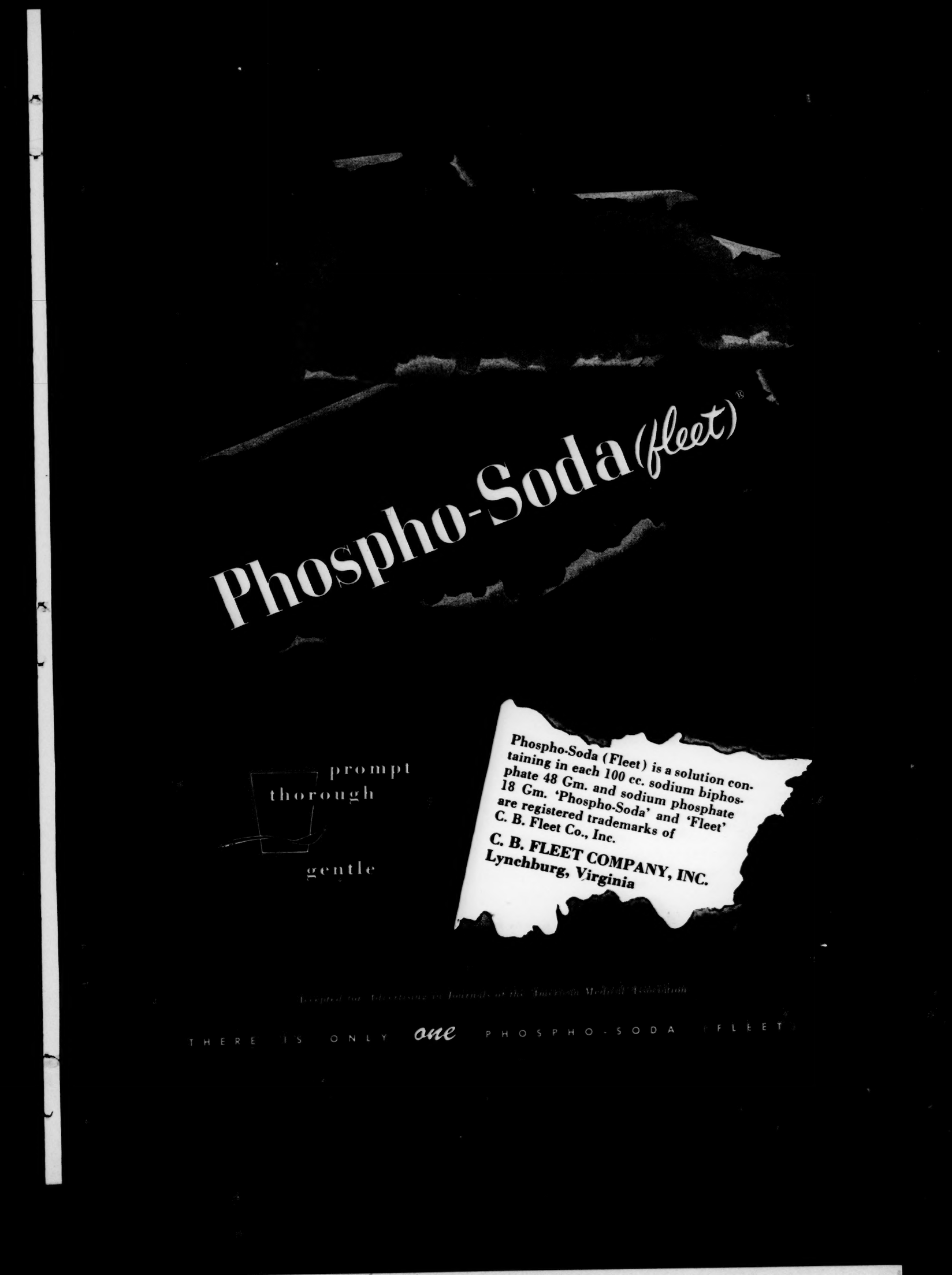
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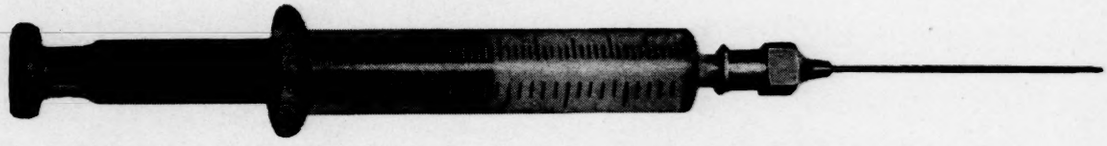

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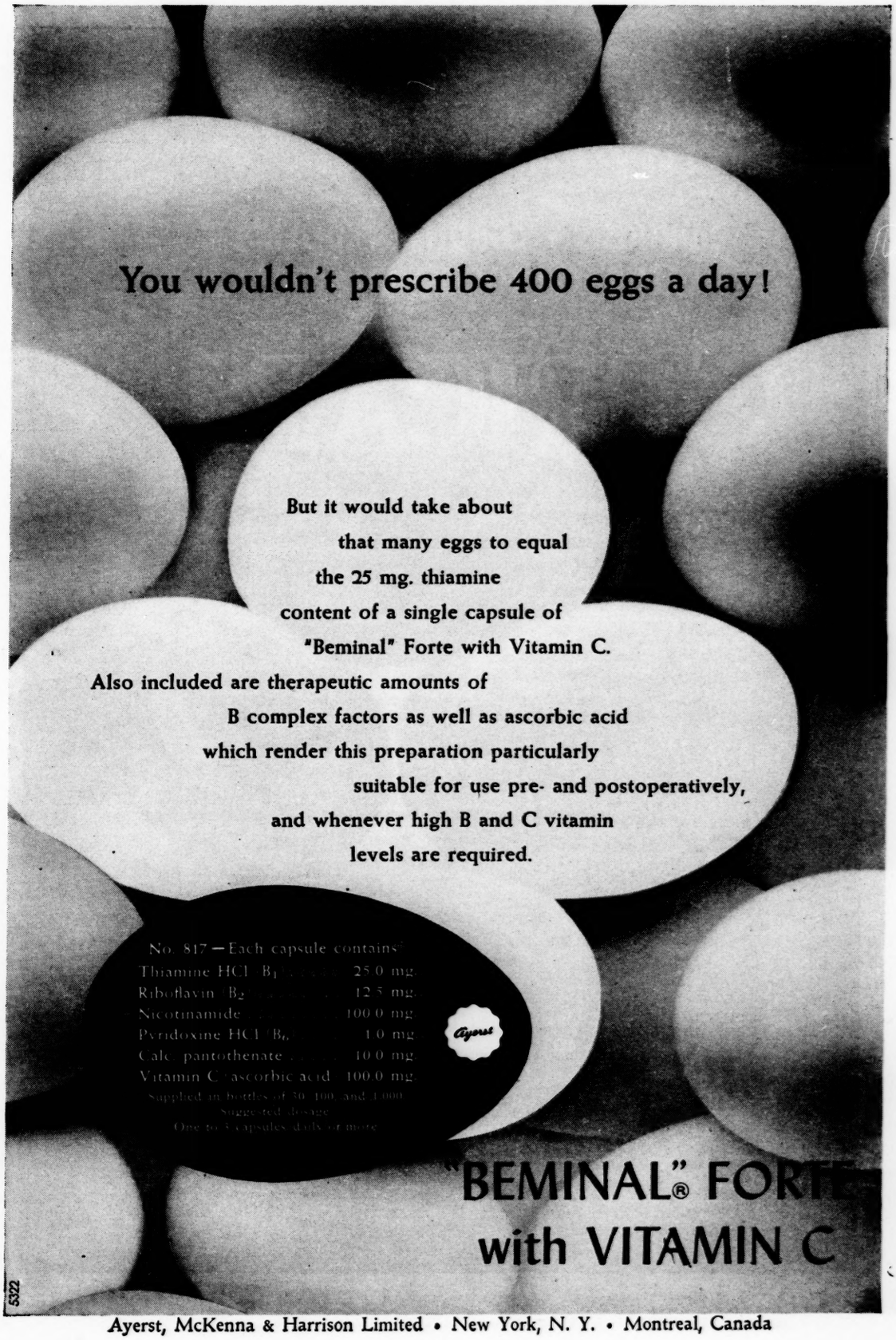
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3. Riseman, J. E. F. N. E. J. Med. 229: 670, 1943.

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3. Sauer, G. C. (1952), J. Missouri M. A., 49:911, November.

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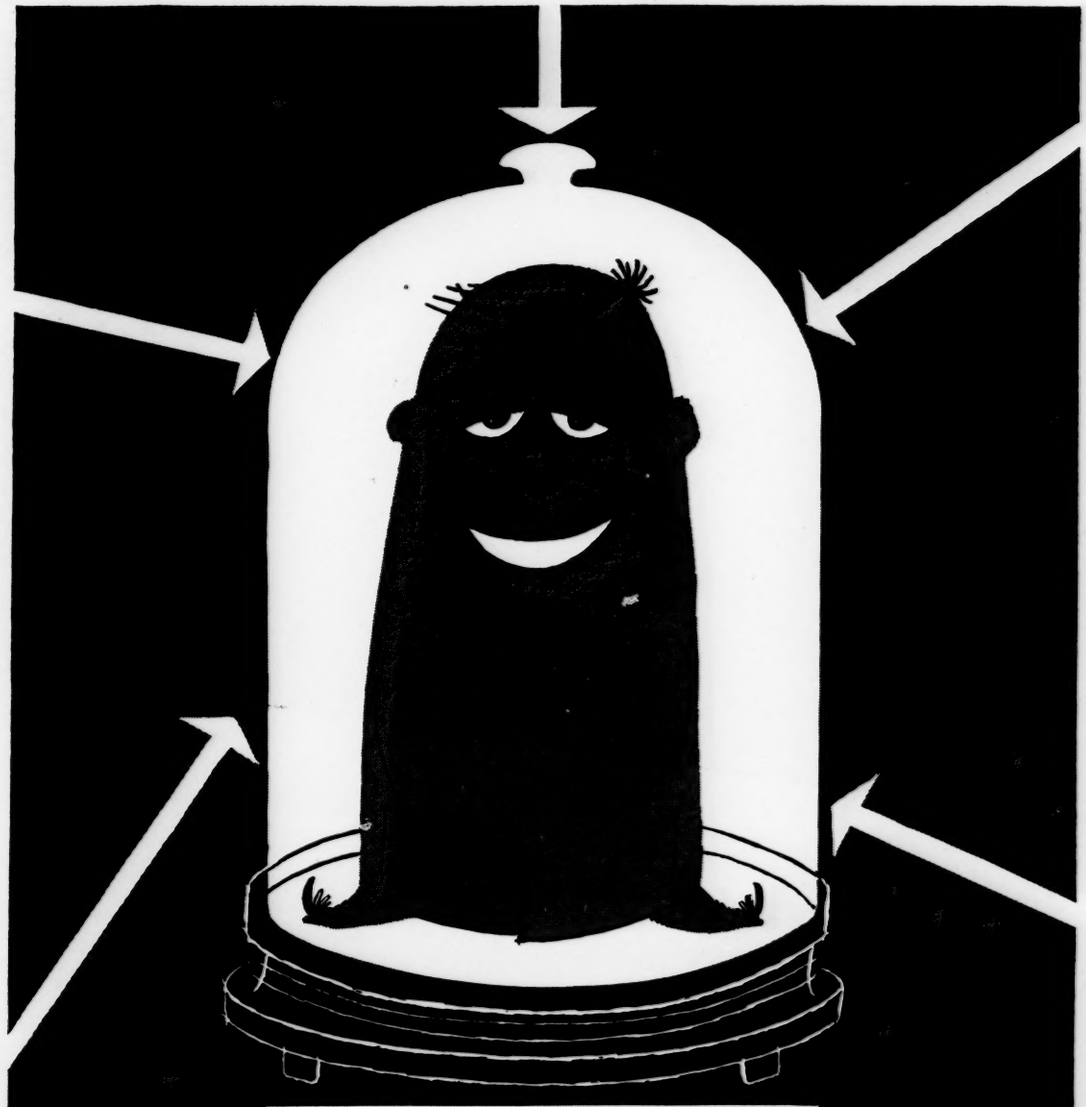

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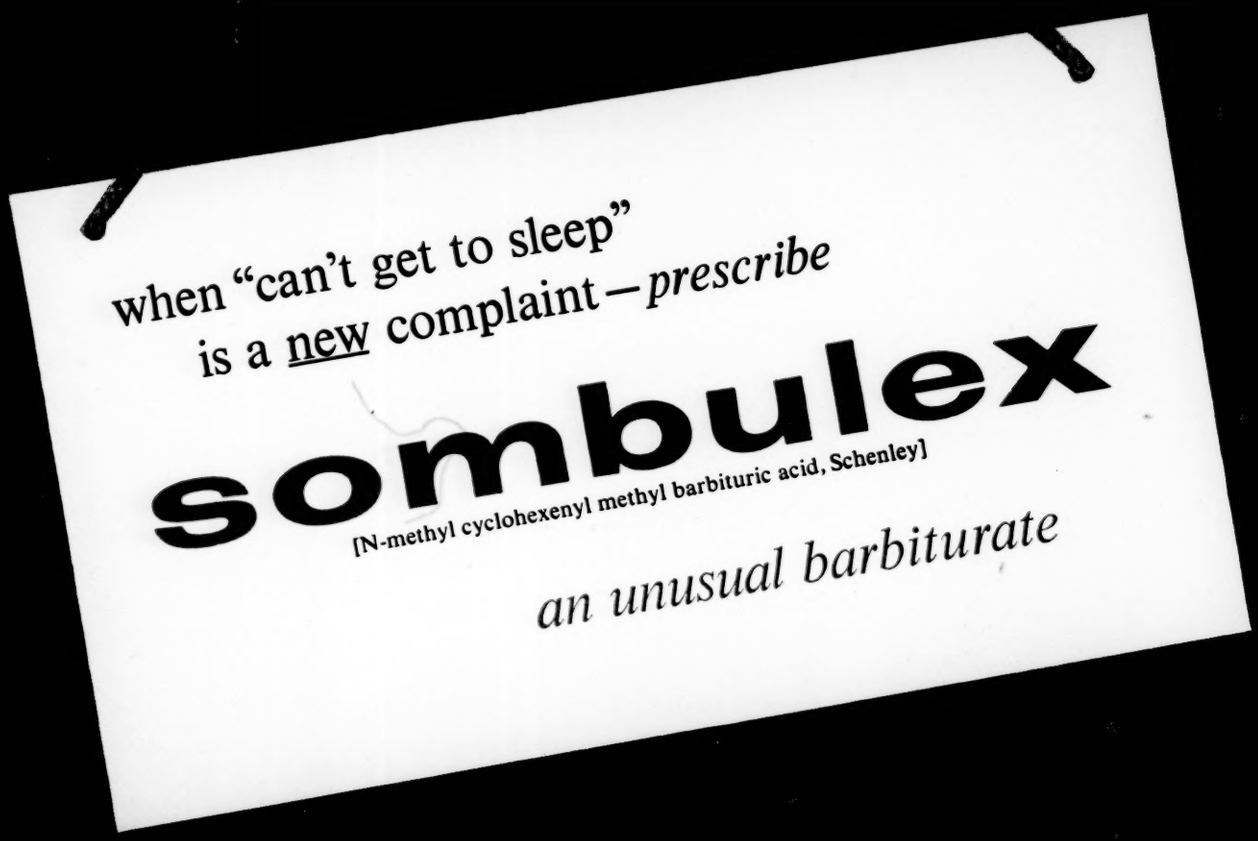
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The American Journal of Medicine

Vol. XV JULY, 1953 No. 1

Editorial

Investigation of the Aging Process

An understanding of the aging process should be of especial interest to the clinician since changes leading ultimately to senility begin relatively early in life and produce alterations in body morphology and function which form the basis for increasing susceptibility to chronic diseases characteristic of the latter half of the human life span. Recently awakened interest in this subject has produced a large and increasing amount of current literature. As one reads the most recent and excellent compilation, the 3rd edition of Cowdry's Problems of Ageing,[1] one is impressed by the fact that despite a considerable mass of data on the anatomic, physiologic and pathologic alterations occurring in old age, coordinated knowledge of physiologic change or changes underlying the aging mechanism is practically non-existent. Promise of more substantial contributions in this respect lies in the increasing number of investigations dealing with fundamental aspects of the problem.

It is the purpose of this brief discussion to indicate certain approaches to the study of the aging process (or processes) which seem to the writer to have special merit. First is that of the reparative or reconstitutive process of cells and tissues, both morphologic and functional. Its importance, emphasized recently by Lansing,[2] lies in the fact that cell death and replacement begins in embryonic life and continues in certain organs throughout life. Even in those organs which possess no capacity for cell replacement, e.g., the brain, reparative processes undoubtedly go on. Yet this subject has received relatively little study, probably for reasons to be noted later. Observations on the reparative capacities of internal organs made by Rous and McMaster[3] and Addis and Lew[4] showed that removal of parts of certain organs or one of paired organs resulted in partial to complete restoration of organ mass, whether or not the animal was still growing, whereas other organs showed no evidence of morphologic restoration. Until recently adequate technics for determination of cellular replacement and repair have been lacking. Now newly developed qualitative and quantitative histochemical and cytochemical methods provide means for a beginning attack on this problem.[5,6] One of the difficulties has been that of actually determining cell loss or gain of a given organ. A cytochemical method recently described by Kurnick[7] makes it possible to determine the number of nuclei in a parenchymatous tissue and offers a means for studying changes in cell number with age.

By means of microspectrography in the ultraviolet and x-ray regions[8,9] it has been possible to localize chemical substances in different parts of a single cell. The next and most important step, namely, the precise quantitative determi-

[1] Lansing, A. I. Cowdry's Problems of Ageing, Baltimore, 1952. 3rd ed. Williams & Wilkins.

[2] Lansing, A. I. Some physiological aspects of ageing. *Physiol. Rev.*, 31: 274–284, 1951.

[3] Rous, P. and McMaster, P. D. Liver requirements of the fasting organism. *J. Exper. Med.*, 39: 425–445, 1924.

[4] Addis, T. and Lew, W. Restoration of lost organ tissue. Rate and degree of restoration. *J. Exper. Med.*, 71: 325, 1940.

[5] Glick, D. Techniques of Histo- and Cyto-Chemistry. New York, 1949. Interscience Publishers, Inc.

[6] Gomori, G. Microscopic Histochemistry. Chicago, 1952. University of Chicago Press.

[7] Kurnick, N. B. Cytochemical studies on the kidney. I. Role of cell multiplication in normal growth. *J. Exper. Med.*, 94: 373, 1951.

[8] Caspersson, T. Cell Growth and Cell Function. New York, 1950. W. A. Norton Co.

[9] Glick, D., Engstrom, A. and Malmstrom, B. G. A critical evaluation of quantitative histo- and cytochemical microscopic techniques. *Science*, 114: 253–258, 1951.

nation of the different intracellular components, is still to be taken and when this is achieved with living material progress in the study of age changes will go forward with great rapidity. Another important aspect of investigation at the cellular level is that of possible changes with age in the transport of metabolic constituents through the cell membrane. Present knowledge of this subject has been admirably reviewed and evaluated by Lowry and Hastings.[10] The possibility that alterations in the permeability of cells for certain ions may exert marked effects on intracellular enzyme systems is suggested by a recent report of Stadtman[11] who found that the activity of phosphotransacetylase is inhibited by Na but potentiated by K salts. Refinements of tissue culture technics as described by Fischer[12] have made possible determination of the metabolic activity and requirements of various cells to maintain life on the one hand and to grow on the other. Such means of separating growth and maintenance offer interesting possibilities of studying cells at different ages.

Another approach for studying individual constitution and the genetics of aging has been opened up by the biochemical studies of R. S. Williams and his group.[13] They found, largely by the use of paper chromatography, that each individual exhibits a distinct and genetically controlled metabolic pattern which conditions his physiologic response to chemical stimuli. Their findings suggest that a number of diseases, including certain mental disorders, may be essentially genotropic in origin.

A promising field of study is that of the effects of diet on aging. Many years ago Child[14] found that restriction of the food intake of planaria resulted in maintaining them in a youthful state for at least three years, while their normal life span is a few weeks. More recently McCay[15a] in an extensive and well controlled study found that the life span of rats could be extended by 100 per cent or more through keeping the animals on diets sufficiently low in calories to prevent full growth. These retarded animals appeared to be much more resistant to the chronic diseases, including tumors, which attack normally fed rats. The particular food constituents, however, which might be most suitable for the restoration of aging tissues are still largely undetermined. Much further work in this area of the problem is needed, particularly in respect to the amounts and kinds of protein desirable.

The relationship of metabolic rate in man to his senescence is still unknown. While it is generally agreed that there is a gradual and progressive decrease in oxygen consumption in the latter decades, the individual exceptions are so frequent as to invalidate conclusions on cause and effect. Rats and dogs in contradistinction to man show no decline in metabolic rate with senescence. Knowledge of changes with age in the various enzyme systems is largely undeveloped, yet these important mechanisms which control utilization of food stuffs may well play a determining role on the rate at which aging occurs.

In contemplating a program of research in this field one is faced with the question as to which of the organ systems would be most profitable to study. While it is quite likely that assembled information on various bodily structures and functions will be necessary to yield a comprehensive picture, three organ systems stand out as exercising control on all parts of the body, namely, the central nervous system, the cardiovascular system and the endocrine organs.

Knowledge of age changes in the brain would seem to be of especial importance in view of the fact that nerve cells appear at best to have limited powers of regeneration. As yet we have relatively little exact data on the aging brain aside from the fact that the number of neurons is observed to decrease with age, the Nissl substance diminishes or disappears and certain other morphologic changes occur whose significance is unknown. There is no precise information as to the numbers of brain cells in different areas at different ages. Does the alert

[10] Lowry, O. H. and Hastings, A. B. Quantitative Histochemical Changes in Ageing. Cowdry's Problems of Ageing, 3rd ed., p. 105. Baltimore, 1952. Williams & Wilkins.

[11] Stadtman, E. R. The purification and properties of phosphotransacetylase. *J. Biol. Chem.*, 196: 527–534, 1952.

[12] Fischer, A. Biology of Tissue Cells. Cambridge, 1946. Cambridge University Press.

[13] Williams, R. S. Individual Metabolic Patterns and Human Disease. University of Texas Publications Biochemical Studies IV, p. 7–22.

[14] Child, C. M. Senescence and Rejuvenescence. Chicago, 1916. University of Chicago Press.

[15a] McCay, C. M. Chemical Aspects of Ageing and the Effect of Diet on Ageing. Cowdry's Problems of Ageing, 3rd ed., p. 139. Baltimore, 1952. Williams & Wilkins.

and active individual of ninety or one hundred years of age possess more normal brain cells than a senile person at seventy? A beginning in this field has been made by Ellis[15b] and Inukai[16] in their quantitative studies of aging human beings and rats. Would the experimental injury and reduction in the number of different kinds of brain cells, produced perhaps by such means as ultrasonic vibration,[17] result in increased rapidity of aging? Study of these and other problems such as the role of the nucleoproteins in the aging of nerve cells may well throw light on the relationship of the brain to declining tissue function.

The cardiovascular system is now being most extensively investigated particularly from the viewpoint of atherosclerosis. Much information is forthcoming from the histologic and histochemical studies of Lansing and co-workers,[18] the physicochemical investigations of lipid metabolism by Gofman,[19] Barr,[20] Turner[21] and co-workers, and numerous others. Of particular importance is the question as to whether repair of damaged arterial walls can take place. Evidence that reversal of degenerative changes is possible has been presented by Kountz[22] who found that administration of estrogens to elderly females resulted in the return to a much more normal appearance of the walls and lumina of the uterine arteries.

[15] (*b*) Ellis, R. S. A preliminary study of the Purkinje cells in normal, subnormal and senescent human cerebella with some notes on functional localization. *J. Comp. Neurol.*, 30: 229–252, 1919.

[16] Inukai, T. On loss of Purkinje cells with advancing age from cerebellan cortex of the albino rat. *J. Comp. Neurol.*, 45: 1–31, 1928.

[17] Wall, P. D., Fry, W. J., Stephens, R., Tucker, D. and Lettvin, J. Y. Changes produced in the central nervous system by ultrasound. *Science*, 114: 686–687, 1951.

[18] Lansing, A. I., Alex, M. and Rosenthal, T. B. Calcium and elastin in human arteriosclerosis. *J. Gerontol.*, 5: 112–119, 314–318, 1950.

[19] Jones, H. B., Gofman, J. W., Lindegren, F. T., Lyon, T. P., Grahm, D. M., Strisower, B. and Nichols, A. V. Lipoproteins in atherosclerosis. *Am. J. Med.* 11: 358–380, 1951.

[20] Barr, D. P., Russ, E. M. and Elder, H. A. Protein-lipid relationship in human plasma. II. In atherosclerosis and related conditions. *Am. J. Med.*, 11: 480–493, 1951.

[21] Turner, R. H., Snavely, J. R., Goldwater, W. H., Randolph, M. L., Sprague, C. C. and Unglaub, W. G. The study of serum proteins and lipids with the aid of the quantity ultracentrifuge. *J. Clin. Investigation*, 30: 1071–1081, 1951.

[22] Kountz, W. B. Degeneration and Regeneration. Cowdry's Problems of Ageing, 3rd ed., p. 882. Baltimore, 1952. Williams & Wilkins.

Knowledge of the role played by the endocrine organs and their hormones in the process of aging is fragmentary even in the case of the thyroid, about which much is known. Yet it is reasonable to assume that these glands must profoundly influence the functional changes which occur as the years progress. Indeed evidence that certain hormones of the anterior pituitary and sex glands injected into mice and guinea pigs can retard or accelerate the aging of the animals' organs and tissues has been provided by the work of Loeb[23] and others. A study of the pituitary growth hormone would seem to offer a profitable subject for investigation since it is generally agreed that aging does not occur until growth, or at least the capacity for growth, ceases. Hence as long as the body can grow, the growth hormone must be available. Certain questions follow. What relationship does the growth hormone bear to the process of repair or reconstitution of cells, organs and tissues? Does the growth hormone diminish with age, resulting in retardation of tissue reconstitution or does the pituitary continue to produce the hormone but response of the tissues diminishes? Bearing on this problem are the studies of Li[24] and associates on the nature of the bodily changes in rats injected with the growth hormone. They found that the chemical composition of the tissues of such treated animals more nearly resembled that of young rats than did the tissues of the untreated controls. Just how the adrenal steroids fit into the age changes is as yet undetermined though there are suggestions that they may be of importance. Administration of ACTH has been shown to retard growth in animals.[24]

Study of aging from the comparative and phylogenetic points of view has already yielded valuable contributions to our knowledge and promises a rich field for further exploration, since it seems likely that the same fundamental metabolic processes operate throughout the various levels of organized living material. The discovery of a clue to the aging process in one form may well provide the key to elucidation of the general pattern of such changes. Among vertebrates and especially mammals the relative slowness of the aging process adds greatly to the difficulties of investigation. Speeding up of aging

[23] Loeb, L. Hormones and the process of ageing. *Harvey Lect.*, 36: 228–250, 1940–41.

[24] Li, C. H. Growth and anterior pituitary. *Growth Symposium*, 12: 47–60, 1948.

such as occurs in certain disorders of the pituitary gland would aid much in this respect. A possible analogous phenomenon is found to occur naturally. Several species of fishes exhibit marked degenerative changes following spawning which end in death within a few days to a week or so. This occurs in the sea lamprey and in all the Pacific salmons. Whether or not such sequence of events represents a telescoping of the aging process remains to be determined. At any rate this phenomenon presents an unusual opportunity for investigation.

Concerning the nature of the changes that occur in the individual cell with progression of the life cycle our information is very meager. Child[14] concluded from an extensive and penetrating study of senescence and rejuvenescence in certain invertebrates that the essential difference between youthful and aging cells is the diminished metabolic rate of the latter. Fischer's[12] observations on cells in tissue culture would agree with Child's conclusions in this respect. The lack of changes in general metabolic rate with age observed among certain species or individuals of more highly organized animal forms does not exclude the occurrence of diminished metabolism in one or more organ or tissue systems which may be masked by the oxidative processes of the body as a whole. Other theories have been advanced but cannot be discussed here. The general inference, however, is that changes leading to senescence are to be sought in individual cells, although the so-called non-cellular tissues should not be neglected. Technics for studying metabolic activities in living undisturbed tissue will have to be developed in order to determine the chemical pattern of intracellular age changes.

It is evident from this very brief discussion that investigation of the fundamental aspects of aging carries implications which go far beyond the problem of senescence. The question may well be asked, why not consider the above outlined studies as pertaining to general life science and let the relationships to aging evolve as they may? The answer is that such an attitude has largely prevailed until quite recently, with the resulting retarded growth of knowledge in this field. The aging process with its many facets is of sufficient interest and importance to attract talented investigators. Skills of chemistry, physics, biology and clinical medicine will be needed and the attack on certain problems will require the combined effort of workers in these several fields.

O. H. Robertson, M.D.

Clinical Studies

The Diagnosis of Mitral Regurgitation*

An Evaluation of Clinical Criteria, Fluoroscopy, Phonocardiogram, Auricular Esophagogram and Electrokymogram

WALTER H. ABELMANN, M.D., LAURENCE B. ELLIS, M.D. *and* DWIGHT E. HARKEN, M.D.
Boston, Massachusetts

SINCE the advent of effective and relatively safe surgical procedures for correction of acquired lesions of the mitral valve,[1–4] the diagnosis of the nature and extent of deformity of the mitral valve has ceased to be of academic interest only and has become important in the selection of patients for operation, in the choice of the type of operation indicated and in the assessment of operative risk and of prognosis.

In the course of evaluation of a series of patients with rheumatic valvular disease for possible surgical therapy it has become obvious that the traditional criteria for the diagnosis of mitral insufficiency do not meet the present need for precise diagnosis. All too frequently a patient who had been thought to have pure mitral stenosis has shown mild to moderate mitral regurgitation at the time of mitral valvuloplasty. There have been instances in which the preoperative clinical diagnosis was mild regurgitation which at operation was found to be marked, and a rare case of unsuspected almost pure mitral insufficiency has come to our attention.

Although sufficient follow-up observations are not available as yet to allow full evaluation of the effect of co-existing mitral regurgitation, it is generally thought that while mild regurgitation may not affect either the operative risk or the prognosis of mitral valvuloplasty, and may even be partially corrected by valvuloplasty,[5] marked regurgitation affects the prognosis unfavorably and is a contraindication to the conventional finger fracture valvuloplasty or commissurotomy.[6–9] Until such time as operations for the correction of essentially pure mitral regurgitation are available that are both effective and safe, the usual practice will continue to be either to defer or to avoid operating on patients whose disability is minor, or to carry out an exploratory cardiotomy in the hope of finding enough mitral stenosis to render the usual valvuloplastic operation helpful. The latter, of course, is an unsatisfactory solution of the problem.

It is the purpose of this communication to review some of the clinical diagnostic findings in a group of patients with rheumatic mitral stenosis who underwent mitral valvuloplasty, with special consideration of the problem of the diagnosis of co-existent mitral insufficiency. The following clinical findings and special diagnostic methods were evaluated as criteria for the diagnosis of mitral regurgitation: The apical systolic murmur; the symptom of easy fatigability; enlargement of the left ventricle; absence of electrocardiographic pattern of right ventricular enlargement or right bundle branch block; marked enlargement of the left auricle; systolic expansion of the left auricle as assessed by fluoroscopy; the auricular esophagogram; the auricular border electrokymogram and the phonocardiogram.

These criteria will be considered individually. Previous reports will be reviewed briefly. The criterion or method used will be described and the results discussed. Some of the physiologic principles, assumptions and limitations underlying these criteria will then be discussed.

CASE MATERIAL

The main group reported consists of sixty-two patients with rheumatic mitral stenosis without

* From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Departments of Medicine and Surgery, Harvard Medical School. Presented in part at the Annual Meeting of the American Heart Association in Atlantic City, April 10, 1953. This investigation was supported in part by a research grant from the National Heart Institute, U. S. Public Health Service.

TABLE I

Case	Age and Sex	Fatigue	Rhythm	Apical Systolic Murmur	RVE		LVE		Left Auricle		Auricular Esophagogram			Findings at Operation				Systolic Blood Pressure	
					X-ray	EKG	X-ray	EKG	Enlargement	Systolic Expansion	Positive Systolic Wave	Systolic Plateau Wave	Amplitude of Plateau mm. Hg	Auricular Thrombus	Estimated MVA cm.²	Mitral Regurgitation		During Cardiotomy	Before Operation
																Before Fracture	After Fracture		
1	26, M		SA	2	++	+	0	0	++						<1	0	+	100	118
2	27, M	3	AF	0	+	±	0	0	+						<1	0		60	100
3	36, F	1	N	0	++	+	0	0	++						<1	0		70	100
4	23, M	3	N	0	+	+	0	0	++						<1	0		50	120
5	46, F	3(2)	N	2(2)	+(+)	0(0)	0(±)	0(0)	+(+)	(++)					1±	0	?	110	130
6	47, M	1	N	3	++		0		++					+	<1	0		100	110
7	31, F	2	N	0	++	+	0	0	++						<1	0		90	110
8	40, F	1	N	3	++		0		++						<1	0			120
9	53, M		N	0	+	+	0	0	++						<1	0		80	114
10	51, F	1	AF	1	+++	+	0	+	+++					+	1±	0		120	140
11	46, M	3(2)	N	1(3)	++(++)	+(+)	0	0	++(++++)	(+++)	(+)	(+)	(25)	+	<1	0	++	155	170
12	30, M	2	N	0	+	+	0	0	+						<1	0		110	130
13	43, M	2	AF	2	+	0	0	0	+					+	<1	0			
14	34, F	1	AF	1	+	0	0	0	+						<1	0		70	95
15	43, F	1(2)	AF	2(4)	(+++)(++++)	0(+)	+(+++)	0(0)	+++(++++)	(+++)				+	±1	+	+	0	
16	26, M	1(1)	AF	2(3)	++++(++++)	0(0)	+(+)	0(0)	++++(++++)	±(±)						+	+++	106	110
17	38, F	3(3)	AF	2(4)	+++(+++)	+(+)	(+++)	0(0)	+++(++++)	(++)	(+)	(±)	(12)	0	<1.0	+++	+++	80	115
18	28, F	2	N	3	++	+	0	0	+++							0		0	100
19	36, F	2	AF	2	++	0	±	0	+++							+			155
20	55, M	3	AF	0	+	+	+	0	+					+	0.5	++			104
21	37, M	2	AF	3	+++	±	0	0	+++						1.4	+++		110	105
22	28, F	3(1)	N	0(1)	+(+)	0(0)	0(0)	0(0)	+(+)	(0)				+	<1	0	0	100	110
23	45, F	3	N	2	+	+	0	0	++	++				0	0.6	0	±	85	
24	41, F	3(1)	AF	1(2)	+(+)	0(0)	0(0)	+(+)	++(++)	(+)				? no	1.0×0.5	++	++	90	124
25	47, M	3(1)	AF	2(3)	+++(++)	+(+)	+(+)	0(0)	+++(+++)	(++)				0	0.9	++	++	98	118
26	38, M	2	AF	0	++	+	+	0	++	+				0	0.8	+	+		130
27	47, F		N	1	+	+	0	0	+	0				0	1.1	0	0	—	110
28	34, M	3	N	0	+	0	0	0	++	0				0	0.7	0	0	80	112
29	33, F	3(1)	N	1(1)	++(++)	+(+)	0(0)	0(0)	++(++)	(0)				0	0.6	0	0		106
30	29, F	4(1)	N	2(2)	++(++)	+(+)	0(0)	0(0)	++(++)	+(+)	(+)	(+)	(3)	+	<1	0	+	70	100
31	37, M	2	N	0	+(0)	0	0	0	++(+)	(0)				0	.9	0	0	150	120
32	27, F	3(0)	AF	3(3)	++(++)	0(0)	0(0)	0(0)	+++(+++)	(+++)				+	1.8	++	+	110	120
33	37, F	2(1)	N	1(1)	++(+)	0(0)	±(0)	0(0)	++(+)	(+)				0	0.6	+	+	80	140
34	40, F	2	N	0	0	0	0	+	++	++						0	+		
35	43, F	3(0)	N	4(0)	+(+)	0(0)	0(0)	0(0)	++(++)	(0)				0	0.5	0	0	90	110
36	22, F	3(0)	N	0(0)	+(+)	0(0)	0(0)	0(0)	++(+)	(+)	(+)	(+)	(8)		1.3	+	++	70	90
37	32, F	3	N	0	+	+	0	++	+					0	1.0×0.3	0	0	80	112
38	42, F	2(0)	AF	0(3)	++(++)	0(0)	+(0)	0(0)	+++(++)	(+)				+	0.8	0	±	110	110
39	44, M	3	AF	4	++	0	+	0	++	++				0	0.7	+++	+++		100
40	41, M	4	AF	3	++	+	0	0	+++	+	+	+	5		1.1	+		100	140
41	43, M	4	N	1	++	+	0	0	++	0	+	+	4		.5	0		90	140
42	39, M	3	N	1	++	0	+	0	++	++	+	+	3	+	.6	+	++	90	115
43	35, M	3	AF	3	++	+	±	0	+++	+	+	+	5	0	2.6	+++	+++	110	
44	25, F	2	N	1	+	0	0	0	+	0	0	0		0	.6	0		70	
45	38, F	4	AF	3	++	+	+	0	+++	+	+	+		0	.8	+		80	
46	45, M	2	AF	1	++	0	0	+	++	++				0	1.7	+	0	140	115
47	20, F	3	N	2	+	0	0	0	++	+	+	0		0	1.0	0	0	80	110
48	46, M	4	AF	3	++	+	0	0	+++	0	+	+		0	.8	++	+	100	110
49	40, M	4	AF	2	++	+	0	0	++	+	+	0		0	1.6	+++		90	116
50	43, F	3	AF	0	+	0	0	0	++	++	+	+		+	.6	+		80	115
51	34, F	3	AF	0	++	±	0	0	+++	0	+	+		+	.3	0		60	110
52	24, F	2	N	0	+	0	0	0	+	++	0	0		0	.3	±		80	115

TABLE I—(*Continued*)

Case	Age and Sex	Fatigue	Rhythm	Apical Systolic Murmur	RVE		LVE		Left Auricle	Auricular Esophagogram			Findings at Operation				Systolic Blood Pressure	
					X-ray	EKG	X-ray	EKG	Enlargement	Systolic Expansion	Positive Systolic Wave	Systolic Plateau Wave	Amplitude of Plateau mm. Hg	Auricular Thrombus	Estimated MVA cm.²	Mitral Regurgitation: Before Fracture	Mitral Regurgitation: After Fracture	During Cardiotomy	Before Operation
53	41, F	2	N	0	0	0	0	0	+	+	0	0		0	1.2	0	0	70	100
54	47, F	2	AF	0	+	0	+	0	+	0	+	0		+	.6	+	+		175
55	42, F	3	N	1	+	0	+	0	+	+	+	0		0	.8	+	+	90	110
56	32, M	3	N	3	+	0	+	0	+	+	+	0		0	2.0	+	+		
57	36, F	4	AF	2	+	0	+	0	+	+	+	0		+	.6	+	+		
58	40, M	2	SB	0	+	0	+	0	+	+	+	0		+	.9	+	+	80	
59	28, M	2	N	3	+	0	+	0	+	+	+	0		0	.7	+	+	100	
60	46, F	4	AF	0	+	0	+	0	+	+	+	0		+	1.9	+	+		105
61	23, F	2	AF	1	+	0	+	0	+	+	+	0		+	.5	+	+		
62	30, M	2	AF	1	+	0	+	0	+	+	+	0		0	.4	+	+		
63	34, M	3(2)	N	1(2)	0(0)	0(0)	0(0)	0(±)	+	(+)	(+)	(+)		0	>2.5	+	+	70	110
64	24, F	4	AF	5	+	0	+	+	+	+	+	+			3.2	+	+	80	130

RVE = Right ventricular enlargement
LVE = Left ventricular enlargement
MVA = Mitral valve area during ventricular diastole
Data in parentheses represent postoperative observations

N = Normal sinus rhythm
SA = Sinus arrhythmia
AF = Auricular fibrillation

significant involvement of other valves, and without clinical evidence of rheumatic activity, who underwent mitral valvuloplasty. Two patients with pure mitral insufficiency have been added to this group (Cases 63* and 64). Table 1 enumerates the pertinent clinical findings and results of special studies individually for these sixty-four patients. Patients 1 to 63 all had a history of progressive disability characteristic of mitral stenosis, all fell into Class III to IV according to the criteria of the New York Heart Association[10] and had a mitral murmur characteristic of mitral stenosis, namely, a low pitched diastolic rumble at the apex with or without presystolic accentuation. At operation, patients 1 to 62 were found to have varying degrees of mitral stenosis, pure or in combination with mitral regurgitation. Patient 63 was found to have pure mitral regurgitation at cardiotomy. Patient 64 died while waiting for surgical correction of mitral insufficiency; the diagnosis was confirmed at postmortem examination.

Mitral regurgitation at time of operation was judged by the surgeon† on the basis of the size and force of the regurgitant jet felt by the exploring finger. It was graded mild (1+), moderate (2+) or marked (3+). If the surgeon's description mentioned "a very marked jet" or "a marked jet with only mild stenosis or none," regurgitation was recorded as 4+. In most instances the surgeon drew a diagram of the mitral valve immediately after the operation. The mitral valve area was measured from this diagram by means of a planimeter and is included in Table 1. In general, the area thus determined has shown good correlation with the mitral valve area measured at postmortem examination. In the earliest cases in this series such diagrams were not made; and inasmuch as the earlier valve descriptions were perhaps less accurate, the patients are numbered in the order of date of operation.

It must be kept in mind that this is a series of patients selected for valvuloplasty. Accordingly, patients with clinically obvious marked or pure mitral regurgitation have been excluded, with the exception of Case 64 as stated above.

Although the surgeon's impression at the time of operation, based on digital palpation and

* We are greatly indebted to Dr. David Littman, West Roxbury Veterans Administration Hospital for the opportunity of studying this patient.

† Dr. Dwight E. Harken except as follows: Dr. John W. Strieder, Cases 39 and 46; Dr. Richard Warren, Case 63.

appraisal, is superior to the traditional postmortem valvular measurements in the assessment of the degree of regurgitation, this method has its limitations. The appreciation of a regurgitant jet is a function of the blood pressure and heart rate prevailing at the time of intracardiac palpation, not to mention the surgeon's sensory threshold and experience. Thus some of the patients described as having no regurgitation at operation may well have some at a blood pressure above or a heart rate below that prevailing at cardiotomy. While these factors may lead to underestimation of mitral regurgitation by the surgeon, the practice of allowing some blood to escape from the auricle may lower the auricular pressure and increase regurgitation at the time of digital palpation.

TABLE II
RELATION OF APICAL SYSTOLIC MURMUR TO DEGREE OF REGURGATION AT OPERATION (SIXTY-FOUR PATIENTS)

Grade of Systolic Murmur	Incidence of Mitral Regurgitation						Total
	0	±	+	++	+++	++++	
0	15	2	5	1	0	0	23
1	8	0	3	2	0	1	14
2	6	0	4	1	2	0	13
3	3	0	2	2	3	1	11
4+	1	0	0	0	1	1	3
0–2+	29	2	12	4	2	1	50
3+, 4+	4	0	2	2	4	2	14
Total	33	2	14	6	6	3	64

A definite regurgitant jet was palpable in twenty-eight of sixty-three patients at the time of cardiotomy. In Table II the distribution of the severity of the regurgitant jet is given.

Certain additional patients were studied in connection with special diagnostic procedures and these will be discussed under the appropriate sections.

THE APICAL SYSTOLIC MURMUR

It is generally taught that an apical systolic murmur of Grade 2 or greater intensity in an individual with other evidence of rheumatic heart disease is indicative of mitral regurgitation.[11–15] It is perhaps not sufficiently appreciated that a loud systolic murmur may be heard at the apex in patients with tight mitral stenosis without significant regurgitation and, conversely, significant mitral regurgitation may be present without apical systolic murmur.[6,16–19]

The auscultatory findings in sixty-four patients with rheumatic mitral disease are enumerated in Table I. The intensity of the apical systolic murmur is described according to Levine and Harvey.[20]

Table II summarizes the preoperative auscultatory findings and relates these to the degree of regurgitation found at operation (or postmortem examination in Case 64). Of the twenty-three patients without systolic murmurs fifteen or 65 per cent showed severe mitral stenosis without palpable regurgitant jet, seven or 30 per cent showed questionable to mild regurgitation in addition to severe stenosis and one patient showed moderate regurgitation with tight stenosis. Of fourteen patients with apical rystolic murmurs of Grade 3 or louder, four so 29 per cent showed no regurgitation at operation, four or 29 per cent showed mild to moderate and six or 43 per cent marked to almost pure regurgitation.

In our experience, then, an apical systolic murmur of Grade 3 intensity or louder in a patient with mitral stenosis suggests mitral regurgitation but does not allow an estimate of its severity, hence by itself is of limited value in the assessment of a patient for mitral valvuloplasty. Significant mitral regurgitation is unlikely in the absence of a systolic murmur at the apex.

MARKED FATIGABILITY

Gorlin et al.[18] reported that all of eleven patients with mitral stenosis and regurgitation had fatigue, tiredness and weakness as their major symptoms, while dyspnea was not a prominent symptom. While this relationship prevailed in a few of our patients with marked regurgitation we have not found it to be general.

The symptom "fatigue" has been graded from 1 to 4+; 1+ indicating slight fatigue, 2+ moderate fatigue, 3+ marked fatigue, with, however, the patient becoming short of breath before feeling tired, and 4+ marked fatigue which precedes and overshadows dyspnea on exertion. It was difficult at times to distinguish the two symptoms, e.g. when tiredness was greatest in the chest

This symptom was evaluated preoperatively in sixty-one patients. There were nine patients who felt that fatigue was not only severe but overshadowed dyspnea. Two of these had no

regurgitation, three had only mild regurgitation while four had moderate to marked mitral regurgitation. Of nine patients with marked regurgitation three complained of fatigue exceeding dyspnea, while five had severe fatigue but even greater dyspnea.

Thus in our patients with pure or relatively pure mitral stenosis marked fatigability is not infrequent. When fatigue overshadows dyspnea one is justified in postulating regurgitation, but on the basis of this criterion alone one should not conclude that regurgitation is the predominating mitral lesion and that valvuloplasty is contraindicated. Such overemphasis of this evidence may deprive some patients of the chance of correction of stenosis.

LEFT VENTRICULAR ENLARGEMENT

It is generally agreed that left ventricular enlargement in a patient with rheumatic mitral disease, in the absence of aortic disease, hypertension or myocardial failure, indicates mitral insufficiency.[21] However, significant mitral regurgitation may be present without clinically detectable enlargement or hypertrophy of the left ventricle. While electrocardiographic criteria for the diagnosis of left ventricular hypertrophy and/or enlargement are fairly well established, the radioscopic diagnosis of slight or moderate left ventricular enlargement in the presence of right ventricular enlargement presents considerable difficulty.

Table III summarizes the preoperative findings in sixty-one patients who were examined radioscopically and radiographically in postero-anterior and both oblique positions, and by means of 12 lead electrocardiograms (Cases 6, 8 and 17 were excluded because of incompleteness of their examinations). The electrocardiographic diagnosis of left ventricular enlargement was based on the criteria of Wilson et al.[22] Radiologic diagnosis of left ventricular enlargement was made when both contour and angle of clearance of the left ventricle were compatible with enlargement of this chamber.

Fifteen patients showed definite left ventricular enlargement or hypertrophy by either electrocardiogram or roentgen examination. All but two of these showed mitral regurgitation. Of these two, one (Case 10) had a blood pressure of 120/70 at the time of palpation of the valve but was one of the earlier cases operated so that a small regurgitant jet might not have been appreciated. The other (Case 34) was thought to have a diastolic thrill to the left of the sternum in the second interspace by some observers but no diastolic basal murmur was heard and she was not considered to have aortic disease; her preoperative blood pressure was 106/60; there is no record of her blood pressure at the time of valvuloplasty. Eight patients with moderate to severe regurgitation failed to show definite evidence of left ventricular enlargement although this was suspected radiologically in three patients.

TABLE III

RELATION OF LEFT VENTRICULAR ENLARGEMENT TO DEGREE OF REGURGITATION AT OPERATION (SIXTY-ONE PATIENTS)

Left Ventricular Enlargement		Incidence of Mitral Regurgitation							
E. K. G.	X-Ray	0	±	+	++	+++	++++	Definite (+- ++++)	Total
None....	None	27	1	5	2	2	1	10	38
None....	Doubtful	2	1	2	0	2	1	5	8
None....	Definite	0	0	6	2	1	0	9	9
Definite .	None	2	0	1	1	0	0	2	4
Definite .	Definite	0	0	0	1	0	1	2	2

Thus in our experience definite left ventricular enlargement or hypertrophy by electrocardiogram and/or radioscopy in a patient with mitral valve disease without aortic disease, hypertension or myocardial failure strongly suggests the presence of mitral regurgitation. Inability to make a diagnosis of left ventricular enlargement or hypertrophy by these means makes significant mitral regurgitation unlikely without ruling it out.

ABSENCE OF ELECTROCARDIOGRAPHIC PATTERN OF RIGHT VENTRICULAR HYPERTROPHY OR RIGHT BUNDLE BRANCH BLOCK

It has been stated that the absence of electrocardiographic evidence of right ventricular hypertrophy in a patient with mitral disease suggests the presence of both mitral stenosis and regurgitation.[18]

The preoperative electrocardiographic findings of sixty-two patients with mitral disease were reviewed with respect to right ventricular hypertrophy and/or right bundle branch block according to the criteria of Wilson et al.[22] All but three patients had roentgenologic evidence of prominence of at least the outflow tract of the right ventricle. The two patients with the most marked regurgitation showed no evidence

of right ventricular hypertrophy or right bundle branch block by electrocardiogram. Both had normal axes and neither showed a pattern of left ventricular hypertrophy. Of six additional patients with marked mitral regurgitation four showed the pattern of right ventricular hyper-

TABLE IV
RELATION OF LEFT AURICULAR ENLARGEMENT TO DEGREE OF REGURGITATION AT OPERATION (SIXTY-FOUR PATIENTS)

Left Auricular Enlargement		Incidence of Mitral Regurgitation						Total
		0	±	+	++	+++	++++	
Mild.....	+	9	1	0	1	0	0	11
Moderate.....	++	20	1	9	1	2	1	34
Marked.....	+++	4	0	4	4	4	1	17
"Giant".....	++++	0	0	1	0	0	1	2

trophy and/or right bundle branch block, one did not, and the remaining one showed an equivocal tracing. Patient number 64 with pure mitral insufficiency showed left ventricular hypertrophy on the electrocardiogram, and combined ventricular hypertrophy at postmortem examination. There were 32 cases without either right bundle branch block or a pattern of right ventricular hypertrophy, of whom 15 showed no evidence of mitral regurgitation at valvuloplasty and 11 showed questionable to mild mitral regurgitation.

In conclusion, while severe mitral regurgitation may be associated with an electrocardiogram which shows no evidence of right bundle branch block or right ventricular hypertrophy, such a tracing frequently occurs in pure mitral stenosis.

MARKED ENLARGEMENT OF THE LEFT AURICLE

Marked dilatation of the left auricle has been considered a sign of mitral insufficiency by some authors[18,23–25] while others have considered it more frequent in mitral stenosis.[26,27] White[21] reports that of twenty-six cases of very large left atria found at postmortem examination sixteen showed mitral stenosis and ten mitral regurgitation without mitral stenosis.

Our findings with respect to the size of the left auricle as seen on preoperative fluoroscopic and radiographic examination of sixty-two patients with mitral stenosis and two patients with pure mitral regurgitation have been summarized in Table IV. Four degrees of left auricular enlargement are distinguished:

Mild	1+	Definite but slight enlargement (oblique view)
Moderate	2+	Moderate deviation of the esophagus posteriorly
Marked	3+	Deviation of the esophagus and in the postero-anterior view the auricle presents on the right cardiac border
Giant	4+	Very marked deviation of the esophagus; the auricle presents both on the left and right in the postero-anterior view ("aneurysm of left auricle")

Of nine patients with marked mitral regurgitation six had markedly enlarged left auricles while three had only moderate enlargement of this chamber. Of the forty-five patients with only slight or moderate left auricular enlargement twenty-nine or 65 per cent had pure stenosis, thirteen or 29 per cent had questionable to moderate regurgitation and only three or 7 per cent had marked mitral regurgitation. Of the nineteen patients with very large auricles four or 21 per cent had pure stenosis, another nine or 47 per cent had mild to moderate regurgitation while six or 32 per cent had marked regurgitation.

A number of patients, who because of the clinical impression of severe mitral regurgitation did not come to operation and are not included in this group, showed marked enlargement of the left auricle, some of them of aneurysmal dimensions. Similarly, a few patients who developed mitral regurgitation after mitral valvuloplasty showed increase in the size of their left auricle.

Thus marked auricular enlargement suggests mitral regurgitation, but it is not unusual in mitral stenosis and may be absent in marked regurgitation.

It may well hold, as Scherf[25] maintains, that the left auricle enlarges earlier in the course of mitral insufficiency than in the course of mitral stenosis, and that a patient with mitral valvular disease and early marked left auricular enlargement has a valve predominantly insufficient, while late in the disease a large left auricle may be present with either marked stenosis or marked insufficiency.

It seems worthy of comment at this point that a characteristic configuration of the left auricle as seen at operation before intracardiac exploration has been associated with regurgitation

fairly consistently by one of us (D. E. H.). This is an auricle with a large appendage and full auricular convexity carrying down to the coronary sinus, which is thus displaced toward or down to the diaphragm. These direct observations would seem to make further roentgenographic studies of auricular configuration desirable.

SYSTOLIC EXPANSION OF THE LEFT AURICLE AS OBSERVED BY FLUOROSCOPY

Roesler[28,29] drew attention to the prominence of left auricular pulsation in patients with marked mitral regurgitation. In cases with very large left auricles, presenting on the right cardiac border, he described an outward movement of the upper right heart border, i.e., an expansion of the left auricle, simultaneous with inward movement of the lower right cardiac border, representing ventricular systole.

This roentgenoscopic sign was extensively studied by Lenègre, Mathivat and Philippe.[30] Fifty-one of sixty-nine patients with rheumatic valvular disease showed retropulsion of the left auricle during systole in the right anterior oblique view, and dextropulsion of the right lower heart border in the postero-anterior view in cases with enlargement of the left auricle to the right. Many of these patients had clinically pure mitral stenosis, and many had no apical systolic murmur.

More recently, Elkin et al.[31] have presented their findings with respect to left auricular motion as observed fluoroscopically in a series of thirty-five patients who subsequently underwent mitral valvuloplasty. Systolic expansion of the left auricle as a sign of surgically evident mitral regurgitation was falsely positive in 40 per cent of the cases and falsely negative in 20 per cent.

In our own fluoroscopic studies on this point our patients were divided into four groups.

Group 1. Forty-eight patients with rheumatic mitral disease, without significant involvement of other valves, about whose mitral valves anatomic information was available. Forty-seven of the patients underwent valvuloplasty, thirty-three of these being studied before and fifteen after operation. One patient died within six months of study and the diagnosis was confirmed at postmortem examination (Case 64). Except for the last case, and Case 63, all patients had some mitral stenosis.

Group 2. Eighteen patients with rheumatic mitral disease, without significant involvement of other valves, who had complete clinical evaluation but no anatomic examination.

Group 3. Seven patients with arteriosclerotic and/or hypertensive heart disease and apical systolic murmurs.

TABLE V

RELATION OF SYSTOLIC EXPANSION OF LEFT AURICLE BY FLUOROSCOPY TO DEGREE OF REGURGITATION AT OPERATION (FORTY-EIGHT PATIENTS) GROUP I

Systolic Expansion	Incidence of Mitral Regurgitation						Total
	0	±	+	++	+++	++++	
0	10	0	1	2	0	0	13
±	0	0	1	0	1	0	2
+	4	1	7	1	1	0	14
++	3	3	3	1	2	1	13
+++	0	0	2	1	1	2	6
Absent or uncertain	10	0	2	2	1	0	15
Definitely present	7	4	12	3	4	3	33

Group 4. An additional group of thirty-seven subjects, comprising six patients with various congenital cardiac lesions and systolic murmurs at the apex, eleven patients with apical systolic murmurs and no evidence of heart disease, i.e., patients with "functional" systolic murmurs, and twenty individuals without murmurs and without heart disease.

All patients were examined fluoroscopically in the upright position, in the postero-anterior and both oblique projections after barium swallow, with held inspiration. Ventricular and auricular motion were observed simultaneously.

The findings in Group 1 are enumerated in Table I and summarized in Table V. Thirty-three patients, or 69 per cent, showed definite systolic expansion of the left auricle, all in the right anterior oblique view with the esophagus filled with barium, and a few with very large auricles also in the postero-anterior projection. Of eight patients with marked regurgitation, seven showed definite systolic expansion of the left auricle, and in one patient expansion was questionable. On the other hand, seven of seventeen patients without demonstrable regurgitation also showed systolic expansion.

One patient with marked regurgitation and uncertain expansion of the left auricle (Case 43)

had ascites and right-sided pleural effusion which made fluoroscopic evaluation rather difficult.

In general, the patients in Group 2 judged clinically to have significant mitral regurgitation showed systolic expansion of the left auricle. Of eleven patients thought to have mitral insufficiency ten showed systolic expansion. However, four of seven patients thought to have pure stenosis also showed systolic expansion.

In Group 3, of seven ambulatory patients with arteriosclerotic and/or hypertensive cardiovascular disease, apical systolic murmurs and left ventricular enlargement, two showed slight systolic expansion of the left auricle which was slightly enlarged in both instances. These two patients were considered to have relative mitral insufficiency confirmed by the finding of systolic expansion of the left auricle.

Of the thirty-seven subjects in Group 4 none showed either enlargement or systolic expansion of the left auricle.

Elkin et al.[31] have pointed out the difficulties and pitfalls of the fluoroscopic method of detection of systolic expansion of the left auricle. Timing of auricular motion with respect to ventricular contraction is difficult when the heart rate is rapid, especially when the auricles contract in normal sinus rhythm. Unsuspected tricuspid regurgitation may conceivably lead to error through transmission of right auricular systolic expansion to the left auricle. As stated previously, patients with obvious tricuspid regurgitation have not been included in this series. It is also conceivable that ventricular enlargement or rotation of the heart might so alter the conditions in the chest that the auricle would be thrust backward in ventricular systole. This might occur in patients with marked right ventricular enlargement with infringement upon the anterior chest wall. Such a backward thrust of the auricle might appear indistinguishable by fluoroscopy from systolic expansion of the auricle. Further discussion of the relation of systolic expansion of the left auricle to mitral regurgitation will follow at the end of this communication.

In our experience systolic expansion of the left auricle when seen on fluoroscopy suggests mitral regurgitation but does not justify conclusions as to its degree, while the absence of this sign does not rule out marked mitral regurgitation. When definite systolic expansion of the left auricle was seen in the postero-anterior view, i.e., pendulum motion of the heart, at least moderate regurgitation was encountered at operation.

The observations in individuals with apical systolic murmurs and without rheumatic heart disease are of interest inasmuch as the finding of systolic expansion of the left auricle in two of seven patients with left ventricular enlargement on the basis of hypertensive and/or arteriosclerotic heart disease, and in none of eleven patients with atypical systolic murmurs and no heart disease suggests that fluoroscopy with attention to the motion of the posterior cardiac border against the barium-filled esophagus may be useful in the evaluation of apical systolic murmurs in individuals who show equivocal enlargement of the left auricle or ventricle.

THE AURICULAR ESOPHAGOGRAM

The pulsations of the left auricle, recorded by means of inflated balloons placed in the esophagus at the level of the left auricle, have been studied intermittently since 1877 when Luciani first mentioned the existence of cardiac pulsations in the esophagus.[33–38] Early technics varied widely and there was no general agreement as to the patterns representing normal or diseased states of the heart. In 1907 Minkowski[34] and Rautenberg[35] independently described a positive plateau curve in the auricular esophagogram of patients with rheumatic mitral insufficiency. Young and Hewlett[36] confirmed the existence of a positive plateau during ventricular systole in the esophagogram of a patient with mitral insufficiency and tricuspid insufficiency but pointed out the difficulties of interpretation of the esophagogram in general because of the widely different patterns found in the normal esophagus at different levels above the diaphragm. Taquini[38] distinguishes four different esophageal pressure curves in the normal, according to the level of the sound. The "ventricular esophageal pulse" is recorded in the lowest portion of the esophagus, the "pure auricular esophageal pulse" is obtained at the level of the lower left auricle, while near the upper border of the left auricle the tracing reflects the impact of the thoracic aorta superimposed upon the auricular pulse, and finally, still higher, the pulse becomes entirely a function of aortic pulsation. In mitral insufficiency the pure auricular pulse shows a large positive

wave occupying all or part of ventricular systole, not found in the tracings of normal individuals. In patients with mitral stenosis, clinically pure, he demonstrated a small, short positive wave early in ventricular systole which led him to postulate that mitral stenosis is always accompanied by some mitral regurgitation.

These and other early studies all utilized air-filled, elastic systems and rubber diaphragms to record the esophageal pressure pulse and, to our knowledge, did not include correlative studies of the esophageal tracings with either direct auricular pressure tracings or with anatomic examinations of the heart. Recently, Lasser and Loewe[39,40] re-investigated the auricular esophagogram, using a water-filled balloon and polyethylene tubing connected to an electromanometer, in a study of dogs before and after experimentally produced mitral insufficiency. These investigators were able to demonstrate that simultaneously registered intra-esophageal and intra-auricular pressure pulses closely paralleled each other in wave contour. They concluded that a semi-quantitative relationship existed between these pulses.

Our own studies in this direction included three groups of patients. Group 1 consisted of twenty-six patients with rheumatic mitral disease in twenty-five of whom the diagnosis was confirmed at operation; twenty of these were studied before and five after valvuloplasty. One patient with pure mitral insufficiency died and the diagnosis was confirmed at postmortem examination. These patients are included in Table 1 with enumeration of their clinical characteristics. Group 2 comprised ten cases of rheumatic mitral disease without anatomic correlation. Group 3 consisted of eight individuals without evidence of abnormalities of heart or lungs.

The method used was essentially that of Lasser and Loewe.[39] Intraesophageal pressure tracings were obtained by means of a small latex balloon of a capacity of about 4 cc., mounted on polyethylene tubing 2 mm. in external diameter and 66 cm. in length. This tube was swallowed by mouth in most instances; in a few cases it was introduced through the nose. The tube was inserted to full length, whereupon the balloon and tube were filled with water, care being taken to eliminate air bubbles as far as possible. A small air bubble as a rule remained in the system. Pressures were measured by means of an electromanometer of the condenser microphone type* and recorded on a multichannel direct writing oscillograph,* along with lead 2 of the electrocardiogram. In a few instances a phonocardiogram or brachial artery pressure pulse were recorded simultaneously. Esophageal pressure curves were recorded with the patient supine, the head being elevated as necessary for comfort, during quiet breathing or more often with breath held in the respiratory mid-position. A tracing was taken with the balloon in the stomach just below the cardia, and followed by tracings at successively higher levels, the tube being withdrawn by 1 to 3 cm. at a time. Initially, the level of the cardia was determined by positioning the balloon under fluoroscopic observation but it was found that when the inflated balloon was drawn up against the cardia a definite tug could be felt, which later served as an indicator of the level of the cardia. In most cases reversal of the intra-esophageal pressure changes with deep respiration as the balloon entered the esophagus from the stomach confirmed the location of the cardia. The pressure curves were analyzed as to contour, amplitude, time of onset, duration and extent along the esophagus of systolic positive waves or plateaus. In a number of patients records were obtained in the left lateral decubitus and sitting position in addition to the standard supine tracings. Records were also taken in held deep inspiration and expiration in several patients.

TABLE VI
RELATION OF AURICULAR ESOPHAGOGRAM TO DEGREE OF REGURGITATION AT OPERATION

Esophagogram	Incidence of Mitral Regurgitation						Total
	0	±	+	++	+++	++++	
Normal	1	2	0	0	0	0	3
Systolic plateau	2	0	7	3	2	3	17
Systolic positive wave without plateau	2	0	1	1	2	0	6

The results obtained in Group 1 have been enumerated in Table 1 and summarized in Table VI. Representative tracings are illustrated in Figure 1. Of seven patients with marked

* Products of Sanborn Company, Cambridge, Mass.

NORMAL SUBJECTS

T. F., Age 29 R. C., Age 28

PATIENTS WITH RHEUMATIC VALVULAR DISEASE

No. 44—Tight M.S.
No M.R.

No. 41—Tight M.S.
No M.R.

No. 45—Marked M.S.
Mild M.R.

No. 48—Marked M.S.
Moderate M.R.

No. 56—Mild M.S.
Marked M.R.

No. 64—Pure M.R.

NSR—Normal sinus rhythm
AF—Auricular fibrillation

MS—Mitral stenosis
MR—Mitral regurgitation

FIG. 1. Auricular esophagograms with simultaneously recorded electrocardiogram. Case numbers correspond to those given in Table 1. The operative findings are indicated below each record. Pressures are indicated in mm. Hg. Since some of the tracings reproduced were taken with respiration suspended, the pressure recorded may not represent the true esophageal pressure; calibrations are given chiefly to indicate the magnitude of cyclic changes.

mitral regurgitation five showed a definite plateau pulse during ventricular systole and often extending into diastole, while two showed a systolic positive wave without true plateau; none had a normal auricular esophagogram. Of twelve patients with mild to moderate regurgitation ten showed a systolic plateau, two showed a systolic positive wave without true plateau, and again none showed a normal pattern. Of seven patients with uncertain or no mitral regurgitation two showed a systolic plateau, two a systolic positive wave, and three had a normal esophagogram. Of the three patients with very marked mitral regurgitation all showed a systolic plateau while two of four patients with marked mitral regurgitation showed a positive wave only.

Thus if the plateau contour is taken as the criterion of mitral regurgitation there were 4 false negatives in the group as a whole and 2 false positives. If, on the other hand, a positive systolic wave is taken as the criterion of regurgitation there were no false negatives but 4 false positives. As has already been pointed out the incidence of regurgitation may well be greater than appreciated by the surgeon's finger, which may account for some of the "false" positives.

The plateau of patients with marked regurgitation tends to show greater amplitude than that of patients judged to have less regurgitation (Table 1) but there are many exceptions. It has not been possible to correlate the duration of the plateau or the extent of its presence along the esophagus with severity of regurgitation. A number of tracings showed a marked dip of diastolic ventricular filling (Fig. 1, Cases 44 and 56) as described by Taquini,[38] but again quantitation has not been feasible.

While minor changes accompanied change of position of the patient or change in respiratory position, the over-all contour of the pressure tracings appeared unchanged.

Ten patients in Group 2 with mitral disease included four patients with clinically predominating mitral regurgitation, three of whom showed the plateau pattern, the remaining one only a positive systolic wave. Three patients with mitral stenosis and mild to moderate regurgitation clinically, all showed plateau tracings, while of three patients with clinically pure mitral stenosis one showed a normal pattern, one a very small positive wave, and only one a plateau wave, which was very short in duration.

The auricular esophagogram in the eight subjects with normal hearts in Group 3 resembled the patterns described by Taquini and others, none of them showing a positive systolic wave or plateau.

The importance of serial tracings along the esophagus from just above the cardia to the level of the arch of the aorta must be emphasized, inasmuch as the question of whether a given tracing represents a pure auricular tracing or an auricular tracing with arterial impact can often only be decided to satisfaction if an aortic tracing is available for comparison.

These observations confirm the existence of an esophageal auricular pressure pulse characteristic for mitral regurgitation and similar to direct auricular pressure tracings reported for dogs by Wiggers and Feil[41] and by Lasser and Loewe[39,40] and for man by Munnell and Lam.[5]

The high incidence of this pattern in patients with mitral stenosis, exceeding the frequency with which a regurgitant jet is felt by the surgeon at valvuloplasty, tends to confirm the contention that most patients with mitral stenosis have some mitral regurgitation.

Efforts to quantitate mitral regurgitation by means of the esophagogram, however, have been very disappointing. In our hands, the esophagogram may tell us when a patient has mitral regurgitation but by itself does not differentiate between regurgitation severe enough to contraindicate valvuloplasty, regurgitation representing the predominating mitral lesion, and regurgitation too mild to be assessed by any other criteria.

As may be seen from Table 1 the esophagogram would seem to be a finer tool with which to appreciate systolic expansion of the left auricle than fluoroscopic observation of auricular motion. In a number of patients who did not show systolic expansion by fluoroscopy but who had regurgitation at operation the esophagogram was positive.

THE LEFT AURICULAR BORDER ELECTROKYMOGRAM

Systolic expansion of the left auricle in patients with mitral valve disease has been recorded by means of roentgenokymography.[42,43] In Heim de Balzac's extensive study[43] characteristic records of mitral regurgitation were described in cases in which the left auricle was markedly enlarged, taking part in the formation of the right or left cardiac border in the postero-anterior view, as well as in cases of lesser auricu-

lar enlargement, when pulsations were recorded in the oblique positions. The plateau of mitral regurgitation was found in cases of clinically pure mitral stenosis as well as in cases of clinical regurgitation.

Following introduction of electrokymography by Henny, Boone and Chamberlain,[44,45] Luisada and Fleischner[46] studied the pulsatory motion of the left auricle by this method. In nineteen of twenty-three patients with mitral valvular disease the auricular border electrokymogram showed a positive systolic plateau which frequently occurred in cases of clinically pure mitral stenosis. A number of subsequent studies of the auricular electrokymogram in mitral disease describe essentially similar findings,[47–51] all recording the pattern of insufficiency as occurring almost always in clinically established regurgitation, often in clinically pure stenosis and never in the normal.

Since none of the previous studies included anatomic or operative descriptions of the mitral valves under study, it was considered of interest to reinvestigate the auricular electrokymogram in an attempt to answer the question whether such tracings are of value in the diagnosis of surgically significant mitral regurgitation. Thirteen patients with rheumatic mitral disease and six subjects without heart disease were studied. Of the thirteen rheumatics three had recently undergone mitral valvuloplasty, five came to operation later, while the remaining five were studied clinically only. The case numbers used in Table VII correspond to similar numbers in Table I.

Border electrokymograms were recorded si-

TABLE VII

RELATION OF AURICULAR BORDER ELECTROKYMOGRAM TO REGURGITATION

Case	Diagnosis	Mitral Regurgitation		Auricular		Border Electrokymogram		
				P-A View		RAO View		
						Posterior Border		
		At Operation	Clinical	Left Border	Right Border	Upper	Mid	Lower
47	RHD	0		?	P	P	P	P
59	RHD	0		V	P	P	—	P
30	RHD	+		V	—	—	PA	P
57	RHD	+		PA	—	P	P	P
55	RHD	++		P	PA	?	P	P
16	RHD	+++		?	P	P	P	—
49	RHD	+++		P	P		P	P
63	RHD	++++		P	V	PA	P	V
G. C.	RHD		±	V	N	P	—	P
D. B.	RHD		++	PA	P	P	P	—
A. W.	RHD		+++	V	V	P	P	P
H. R.	RHD		++++	V	P	—	P	P
N. N.	RHD		++++	P	P	P	P	P
F. A.	No HD			N	N	—	N	—
D. D.	No HD			N	N	PA	N	N
D. C.	No HD			N-PA	N	PA	N	N
A. D.	No HD			N	N	N	N	V
A. D.	No HD			N	N	P	N	V
S. S.	No HD			N	P	N	P	V

Legend:
N = Normal left auricular pattern
PA = Pulmonary artery
RAO = Right anterior oblique
RHD = Rheumatic heart disease
? = Indefinite
P = Plateau
V = Ventricular pattern
— = Technically unsatisfactory

multaneously with the carotid pulse by means of the improved electrokymograph described by Henny, Boone and Chamberlain.[45]* The subject stood at ease during the examination. Electrokymograms were recorded with respiration suspended in the mid-inspiratory position. With the subject in the postero-anterior position, tracings were obtained from the aortic knob, pulmonary conus, just below the pulmonary conus (? left auricular appendage), left ventricle, right mid-border, right lower border. The subject was then rotated into the left anterior oblique position and tracings were taken from the ascending aorta, lower anterior heart border and lower posterior border. The position was then changed to the right anterior oblique and electrokymograms were recorded from the posterior heart border, high, mid and low.

The results are summarized in Table VII. Representative tracings are illustrated in Figure 2. Patterns corresponding to normal auricular border tracings reported in the literature are labeled "normal," while patterns of the plateau type described as typical for mitral regurgitation are labeled "plateau." Typical plateau curves were recorded in all patients with rheumatic mitral disease. With the exception of one patient (Case 30) with pure mitral stenosis at operation in whom the surgeon thought that valvuloplasty produced some regurgitation, and who at postoperative study showed a typical plateau curve in only one lead, all rheumatic patients showed plateau curves in 2 to 5 leads. On the basis of the auricular border electrokymogram it was not possible to distinguish the patients with pure stenosis from those with marked regurgitation. Two of the six control subjects without evidence of heart disease showed typical plateau curves in one or two auricular border tracings.

The most surprising and methodologically discouraging finding in this small series was the presence of systolic plateau patterns in the border electrokymogram of subjects without heart disease. That we are not dealing with a very rare finding is evident from two very recent electrokymographic studies. Dussaillant et al.[52] found patterns of systolic expansion not infrequently in the auricular border electrokymograms of normal subjects as well as of patients

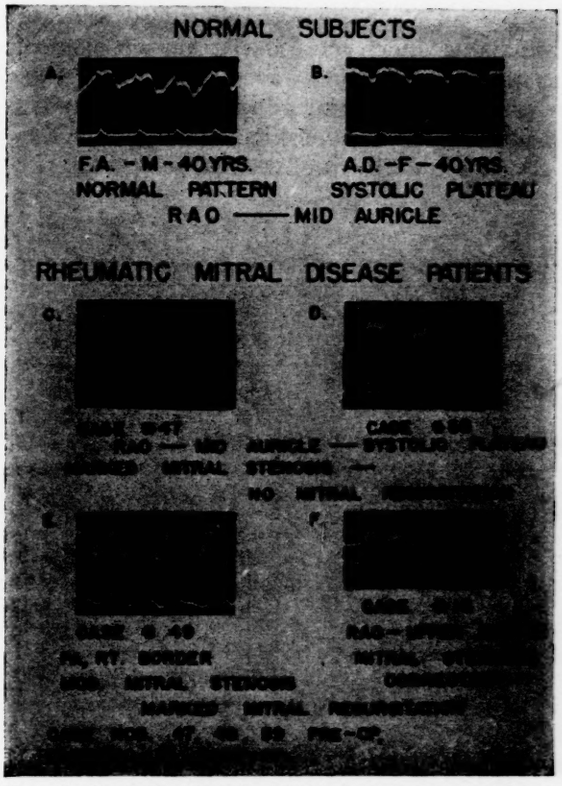

FIG. 2. Auricular border electrokymograms recorded above carotid pulse. Case numbers correspond to those given in Table I. RAO = right anterior oblique position; PA = postero-anterior position.

with heart disease without evidence of involvement of the mitral valve. Such plateau curves unrelated to mitral valve disease were never seen in more than one lead, while the systolic plateau of mitral regurgitation could be obtained consistently from all left auricular leads irrespective of position of the patients. Soloff et al.[53] studied a group of fifteen subjects without heart disease by means of border electrokymograms at 1 cm. intervals in different projections and found "typical plateau curves" in ten, of which two showed such tracings in more than one projection. However, these investigators also report that plateau curves are more frequently and more consistently obtained from patients with disease of the mitral valve.

A number of factors may conceivably contribute to the formation of such "false" plateau tracings. The upward motion of the healthy mitral leaflets during closure may result in slight increase of intra-auricular pressure but can hardly be credited with producing sustained systolic expansion of the auricle, visible in some

* We are greatly indebted to Dr. Thomas R. Dawber, Director of Framingham Heart Clinic, for placing the electrokymograph at our disposal, and to Mr. William Claffy for technical assistance.

but not all electrokymographic derivations. It would seem much more likely that we are dealing with a summation wave produced by aortic or pulmonary arterial pulsations superimposed upon auricular and ventricular motion, or then with mass movement of the heart.

TABLE VIII

RELATION OF PHONOCARDIOGRAPHIC MEASUREMENTS TO DEGREE OF REGURGITATION AT OPERATION

Case	Status	Mitral Regurgitation at Operation (or Postmortem)	Interval QRS − S_1				Interval S_2 − OS			
			No. Cycles	r	SE	Sign 5% Level	No. Cycles	r	SE_r	Sign 5% Level
51	Preop.	0	26	−0.54	0.20	Yes				
62	Preop.	0	36	−0.36	0.17	Yes	36	+0.29	0.17	No
54	Preop.	±	22	−0.75	0.22	Yes	22	+0.93	0.22	Yes
40	Preop.	+	61	−0.47	0.13	Yes				
45	Preop.	+	17	−0.30	0.25	No				
50	Preop.	+	24	−0.30	0.21	No	12	+0.73	0.31	Yes
57	Preop.	+	42	−0.13	0.16	No				
11	Postop.	++	18	−0.15	0.24	No				
32	Preop.	++	23	−0.23	0.21	No				
48	Preop.	++	31	+0.10	0.18	No				
17	Postop.	+++	38	−0.42	0.16	Yes	25	+0.93	0.20	Yes
39	Preop.	+++	24	+0.01	0.21	No				
49	Preop.	+++	40	−0.67	0.16	Yes				
60	Preop.	+++	23	−0.63	0.22	Yes	13	−0.12	0.29	No
64	6 mo. antemortem	++++	44	+0.71	0.15	Yes				

Thus the qualitative auricular border electrokymogram in our hands has not contributed to the diagnosis and quantitation of mitral regurgitation in patients with rheumatic valvular disease. It remains possible that in different technical arrangement and with more precise positioning and exploration electrokymography may yet become useful in this problem.

THE PHONOCARDIOGRAM

As a graphic record of murmurs the phonocardiogram has not been of assistance in the evaluation of patients for valvuloplasty in this clinic.

This section will deal with the timing of heart sounds, as recorded by the phonocardiogram, in patients with variable degrees of mitral stenosis and insufficiency. Luisada[54] has shown that in patients with mitral stenosis and auricular fibrillation the first heart sound following a short cycle may be delayed, and Margolies and Wolferth[55] have found that in similar patients the interval between the second heart sound and the opening snap varies with the preceding cycle length. Messer et al.[56] recently analyzed the phonocardiograms of five patients with severe mitral stenosis and auricular fibrillation. These investigators confirmed the observation that the interval between the second heart sound and the opening snap varies with the length of the preceding cycle, while the interval between the onset of electrical systole and the first heart sound varies inversely with the length of the preceding cycle. They attributed these variations to change in the atrioventricular pressure gradients with change in cycle length. Kuo and Schnabel[57] confirmed these relationships in patients with uncomplicated mitral stenosis but report that both intervals remain fixed when mitral stenosis is accompanied by either mitral or aortic regurgitation.

In our own studies fifteen phonocardiograms were taken in fifteen patients with pure mitral disease and auricular fibrillation and known operative or postmortem findings. Table I enumerates the clinical characteristics of these patients.

Phonocardiograms were taken by means of a Stethocardiette[58]* simultaneously with lead 2 of the electrocardiogram. The time interval between the onset of the upstroke of the R wave of

* Product of Sanborn Company, Cambridge, Mass.

the electrocardiogram and the first major vibrations of the corresponding first heart sound was measured and correlated with the duration of the preceding cycle length, i.e., the R-R interval. If the opening snap was clearly registered, which was the case in five tracings, the time interval between the first main vibration of the second heart sound and the beginning of the opening snap was measured and similarly correlated with the duration of the preceding cycle.

The results are given in Table VIII. While two cases of pure mitral stenosis (Nos. 51 and 62) suggest negative correlation between the interval QRS-S1 and the length of the preceding cycle, similar correlation was shown by three cases of marked mitral regurgitation (Nos. 17, 49 and 60). Of the latter, patient No. 60 at time of operation was judged to have very little stenosis, and represents the type of patient who, if the valve could be assessed correctly without cardiotomy, would not be a candidate for valvuloplasty. One patient with pure insufficiency (No. 64) as well as one patient with stenosis and definite regurgitation (No. 40) showed positive correlation of the interval QRS-S1 with length of the preceding cycle.

In only five tracings was an opening snap of sufficient clarity recorded to allow measurements. A patient with pure stenosis (No. 54) showed high positive correlation between the interval S2 and OS and the length of the preceding cycle, but so did a patient with marked postoperative mitral regurgitation (No. 7). The data confirm the variation of the time intervals QRS-S1 and S2-OS in some patients with mitral valvular disease and auricular fibrillation, with a tendency for negative correlation of the interval QRS-S1 with the length of the preceding cycle, and a positive correlation between the interval S2 and OS and the length of the preceding cycle. While in some patients with moderate to marked mitral regurgitation these correlations were reversed in sign, such was not the case in others. Thus, in our hands, analysis of these time relationships on the phonocardiogram did not lend itself as a useful test for mitral regurgitation. The number of cycles available for measurement, however, was small in several of the tracings reported here; and thus the possibility exists that analysis of larger numbers of cycles might alter the correlations.

While our studies do not allow conclusions as to the mechanism of these variations in time relationships, it would seem that in addition to the variation in left auricular pressure with cycle length, the variation of intraventricular pressure with cycle length must be considered as a factor in determining the time of opening and closure of the valves. Also, mechanical systole may conceivably vary in time of onset and in course with the degree of ventricular filling, as suggested by the observation that the duration of mechanical systole may vary with the duration of the previous cycle.[54]

DIAGNOSIS OF MITRAL REGURGITATION BY COMBINATION OF CRITERIA

In order to determine if a combination of criteria would render the diagnosis of mitral regurgitation more dependable than that based upon any one single criterion, the degree of mitral regurgitation found at operation has been correlated with the following clinical criteria singly and in all possible combinations: apical systolic murmur, grade 3 or more; marked left auricular enlargement; left ventricular enlargement and systolic expansion of left auricle by fluoroscopy. When this was done for the group of forty-seven patients with mitral stenosis on whom fluoroscopic observations of auricular pulsations were available it was found that any two of the above four criteria were met by five of seven (71 per cent) patients with marked regurgitation, by twelve of nineteen (63 per cent) patients with mild to moderate regurgitation, by one of four (25 per cent) patients with questionable regurgitation, and by only one of seventeen (6 per cent) patients with pure stenosis. This represents the formulation of criteria which yielded the smallest number of false negative and false positive diagnoses in this series.

COMMENTS

It is evident from the previous sections that in our hands no physical finding and none of the special tests discussed, when considered alone, has been proven reliable in the quantitation of mitral regurgitation in patients with mitral stenosis. As stated previously, the clinical need demands that mild regurgitation be differentiated from marked regurgitation, the latter being a relative contraindication to present day operative treatment of mitral stenosis, while the former is not.*

* The relative merits and problems associated with the less successful surgical treatment of mitral insufficiency are not considered germane to this discussion.

Some of the possible errors and limitations of the various criteria evaluated have already been discussed. Some aspects of the hemodynamics of mitral regurgitation will now be considered in more detail in order to attempt to understand why quantitation of mitral regurgitation by the methods discussed meets with such difficulty.

Apical Systolic Murmur. The intensity of a murmur is determined by the change in size of the lumen through which blood flows, by the velocity of the blood flow, by the viscosity of the blood, and by the ability of the parts that produce the murmur to vibrate.[11] The velocity of blood flow in turn is a function of differential pressure and size of the lumina concerned. Thus it is understandable that the loudness of the apical systolic murmur in a given patient may not vary directly with the mitral valve area, or with the force of the regurgitant jet, and that a patient with "tight mitral stenosis," without palpable regurgitant jet, may have a loud systolic murmur (e.g., Cases 6, 18, 35) produced by regurgitation of a small amount of blood through a narrow orifice at high pressure. Conversely, the wide open valve of pure mitral insufficiency may offer little obstruction to the regurgitant flow and may not give rise to a significant murmur. This is exemplified by patient No. 63 with essentially pure mitral regurgitation who preoperatively showed a Grade 1 systolic murmur at the apex which was heard only intermittently.

Systolic Expansion of the Left Auricle, As Evaluated by Fluoroscopy, Esophagogram or Electrokymogram. These diagnostic procedures are all concerned with the appraisal of changes in the volume of the left auricle. A number of variables determine the production and degree of systolic expansion of the left auricle by a regurgitant jet of blood through an incompetent mitral valve. The degree to which intra-auricular pressure and auricular volume are increased by regurgitation will first of all depend on the amount of reflux blood that enters the chamber. The extent to which a given amount of blood added to the auricle increases intra-auricular pressure and/or auricular volume is a function of the elastic properties of this chamber, which in turn are determined by its size and shape, by the thickness and rigidity of its wall and possibly also by presence or absence and size of mural thrombi. It is conceivable that inflammatory changes in the auricular wall, such as have been found frequently in auricular biopsies taken at the time of valvuloplasty,[59–62] may play a role. Furthermore, the auricle can hardly be considered an isolated chamber since it is continuous with the pulmonary venous system. Thus the elastic properties of the pulmonary veins as well as the degree to which these are filled become determinants of the reaction of the left auricle to blood regurgitated. Opdyke et al.[63] have shown that in the normal dog the smaller left atriovenous system has a greater volume-elasticity coefficient, i.e., is more rigid, less distensible than the larger, thinner-walled right atriovenous system. Thus it may not be unreasonable to postulate that as the left auricle enlarges in mitral valvular disease, and as its wall is thinned, its volume-elasticity coefficient must decrease, i.e., the auricle becomes more distensible. That this must be so can also be derived from Laplace's formula[64] for a hollow sphere:

$P = 2T/r$, where P is the pressure difference across the wall, T the tangential tension in the wall, and r the radius. Thus an increase in the radius of a spherical chamber results in considerable increase in the tension of the wall with only a small increase in pressure.

In view of these considerations one may not be justified in assuming that a small amount of regurgitation into a small auricle may produce marked systolic expansion, while the same amount of blood entering a large auricle may produce little or no increase in volume; or conversely, that marked systolic expansion of a small auricle may represent but mild regurgitation while marked pulsation of a large auricle must indicate marked regurgitation. If these assumptions often appear verified by the operative findings and seem borne out in general by the data reported here, this may be attributable to the role of regurgitation in the development of a large auricle. It is conceivable that the large auricle of some cases of pure stenosis dates back to a time when stenosis was only moderate and regurgitation marked.

Another factor which must be considered a determinant of changes in auricular pressure and volume during ventricular systole is the pulmonary venous inflow. This accounts for the gradual rise in intra-auricular pressures during systole found in curves obtained from normal animal and human subjects.[5,39–41] It is possible that if the output of the right ventricle is great,

the venous inflow to the left auricle may be more rapid during ventricular systole and produce systolic expansion. This could conceivably occur in mitral stenosis in which the pulmonary artery pressure is increased and the capacity of the pulmonary vascular bed limited.[65–67]

Slight increase in auricular pressure might also result from the upward motion of the healthy mitral leaflet during closure.[68] While this impact of the mitral valve may conceivably produce slight brief retropulsion of the left auricle and thus perhaps account for an occasional abnormal auricular electrokymogram or esophagogram, it is difficult to conceive that it could produce retropulsion of sufficient magnitude and duration to be visible during fluoroscopic examination.

Some of these factors may also have a bearing on the difficulties encountered in assessing mitral regurgitation by means of analysis of pulmonary "capillary" pressure tracings obtained during cardiac catheterization according to the method of Hellems et al.[69] While initially a high V wave occurring unusually early in the cycle gave hope of allowing preoperative diagnosis of marked mitral regurgitation,[70–72] it became increasingly evident that the pattern of the pulmonary "capillary" pressure tracing does not allow quantitation of mitral regurgitation and may be unremarkable in presence of marked or even pure regurgitation.[18,67,73] Of pertinence to this problem are Ankeney's recent studies[74] of pulmonary capillary pressure tracings in dogs, which seriously challenge previous concepts of such tracings as reflecting pressure changes in the pulmonary capillaries, veins and left auricle. It is also of interest that Wynn et al.[75] were able to relate direct left auricular pressure patterns, obtained before and after mitral valvuloplasty, to the presence and degree of mitral regurgitation in but a few of the patients so studied.

Notwithstanding our failure to find a single valid criterion for the diagnosis of marked mitral regurgitation in patients with rheumatic mitral disease who are being considered for operation, we are confident that in the great majority of patients adequate preoperative appraisal is possible. To this end, all data available must be considered and weighed according to their merits. Given a patient with typical history and findings of mitral stenosis and disability of a degree indicating operation, an apical systolic murmur of Grade 2 or less, a left auricle moderately enlarged in posterior direction only, evidence of right ventricular enlargement by x-ray or EKG without evidence of left ventricular enlargement, and showing definite but slight systolic posterior expansion of the left auricle by fluoroscopy, kymogram or esophagogram, one may be reasonably certain that no mitral regurgitation of a degree that would contraindicate valvuloplasty is present. Definite evidence of left ventricular enlargement, either by EKG or x-ray, in absence of aortic disease, hypertension or myocardial failure, makes one suspect moderate mitral regurgitation. At least it leads the physician to be cautious in his postoperative prognosis. If it is associated with any or several of the other presumptive signs of mitral regurgitation, such as a very loud apical systolic murmur, marked left auricular enlargement with systolic expansion, and symptoms of fatigability and weakness overshadowing dyspnea, it has been our policy to consider regurgitation marked and probably the predominant mitral lesion. An occasional patient in this situation is anxious to take the risk of exploratory cardiotomy, while the majority are being treated medically in the hope that a safe operation to correct mitral regurgitation may become available in the near future.

The question of the effect of co-existing mitral regurgitation upon the operative risk and prognosis of the operation for mitral stenosis will be dealt with in subsequent reports of follow-up observations on a larger group of patients. A preliminary follow-up survey of the patients reported here, however, supports our impression that mild to moderate regurgitation does not preclude benefit from mitral valvuloplasty for stenosis. Of the twenty patients with mitral stenosis and mild to moderate regurgitation, three have died; one of these, Case 46, was improved by the operation but died later of inoperable carcinoma of the lung; one has been followed for less than six months, sixteen have been followed for six to twenty-nine months. Of these latter, one is worse with residua from a cerebral embolus, one is slightly improved, six are moderately improved and eight show marked improvement. Of seven patients with mitral stenosis and marked regurgitation, one died, and six have been followed for eleven to twenty-six months. Of these six, one remains unchanged, 3 are moderately improved, and two are markedly improved.

SUMMARY AND CONCLUSIONS

1. Fatigability, apical systolic murmur, heart chamber enlargement, systolic expansion of the left auricle on fluoroscopy, auricular border electrokymogram and esophagogram, as well as the relationship of the timing of heart sounds in respect to cycle length as shown by the phonocardiogram, have been evaluated as criteria in the diagnosis of mitral regurgitation in patients with rheumatic mitral disease. Of the patients studied, sixty-three came to valvuloplasty and operative descriptions of the mitral valve were available.

2. Mitral stenosis was found to be accompanied by insufficiency of varying degree more often than generally held and clinically suspected.

3. Marked mitral regurgitation may exist with but a faint apical systolic murmur and, conversely, tight mitral stenosis may be accompanied by a loud apical systolic murmur. In general, however, a systolic murmur of Grade 3 or louder at the apex indicates moderate to marked mitral regurgitation. By itself, a loud apical systolic murmur does not contraindicate valvuloplasty for stenosis.

4. Severe fatigability and weakness overshadowing dyspnea is often associated with marked mitral regurgitation but may be found in patients with predominantly mitral stenosis and may be absent in marked mitral regurgitation.

5. Definite left ventricular enlargement demonstrated either by radiography and fluoroscopy or in the electrocardiogram in the absence of aortic valvular disease, hypertension or myocardial failure speaks for predominant mitral regurgitation, although marked stenosis may occasionally coexist.

6. Aneurysmal dilatation of the left auricle indicates marked to predominant mitral regurgitation, while very large left auricles may on occasion be seen with mitral stenosis as the predominant lesion.

7. Definite systolic expansion of the left auricle on fluoroscopic examination when seen in the postero-anterior projection is presumptive evidence of marked mitral regurgitation. In the oblique position this sign may be present in tight mitral stenosis and it may be absent in marked mitral regurgitation. It has not been seen in patients without heart disease or in patients with functional apical systolic murmurs.

8. The auricular esophagogram, while a more sensitive method of recording systolic expansion of the left auricle, and occasionally of clinical value, has not improved clinical quantitation of mitral regurgitation in our hands.

9. Auricular border electrokymograms showed plateau tracings reportedly characteristic of mitral regurgitation in all patients with mitral disease. Similar patterns were seen in subjects without heart disease although less frequently and less consistently.

10. Phonocardiograms of a small group of patients with mitral valvular disease with auricular fibrillation confirmed the tendency of the Q-S_1 interval to vary inversely with the duration of the preceding R-R interval, and of the S_2-OS interval to vary with the preceding R-R interval in pure mitral stenosis. In the presence of mitral regurgitation these correlations were at times abolished or inversed. The findings did not appear sufficiently consistent to be of diagnostic value.

11. The possible hemodynamic and technical causes of the difficulties encountered in correlating systolic expansion of the left auricle as assessed by fluoroscopy, esophagograms and electrokymograms with the degree of mitral regurgitation have been discussed.

12. The feasibility of correct preoperative diagnosis of marked mitral regurgitation in most cases of mitral valvular disease under consideration for valvuloplasty is reasserted. No single criterion may be relied upon; consideration of all clinical findings usually allows correct assessment of the individual patient.

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Early Changes of Mitral Valve Function in Rheumatic Heart Disease*

A Clinical, Phonocardiographic and Electrokymographic Study

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EVALUATION of the possible myocardial or valvular damage caused by rheumatic fever is not always easy and, in particular, evaluation of valvular dysfunction is difficult in the early stages of this disease. Nevertheless, prognosis after the first attack and diagnosis and therapy after recurrences are greatly influenced by the recognition of valvular lesions and estimates of their severity.

At present, recognition of myocardial lesions is based largely upon electrocardiographic data and on the occurrence of heart failure; judgment of valvular lesions, on finding of murmurs upon auscultation. However, as long ago as 1924[1] it was stated that the murmurs heard during an acute attack of rheumatic fever are "functional" while "organic" lesions develop, if they do appear, slowly in subsequent months or years.

The present study was made with the conviction that re-evaluation of this problem with the help of newer technics was indicated and that a correlation between clinical data and graphic findings might shed some light upon the problem of the onset of mitral regurgitation and mitral stenosis in rheumatic subjects.

Previous Studies. Studies of the systolic murmurs in the early stages of rheumatic fever have been based mostly upon subjective, auscultatory data. In general, there is agreement that a systolic murmur is not sufficient for the diagnosis of cardiac involvement in rheumatic fever,[2] and can be considered only presumptive evidence of valvulitis.[3] This because "it is impossible to distinguish between a *functional* and an *organic* murmur.[4,5] On the other hand, it is admitted that an organic murmur over either the mitral or the aortic valve areas can appear within a few weeks after the onset of rheumatic fever.[4] Several authors consider the early systolic murmur of rheumatic fever as evidence of myocarditis causing dilatation of the mitral ring[5–8] while others consider that it is due to edema of the leaflets, e.g., to initial endocarditis.[9] It should be added that a systolic murmur, which is variously described as either soft[10] or harsh,[8] frequently appears over the pulmonary area and was attributed to either rheumatic involvement of the pulmonic ring[10] or dynamic distention of the pulmonary artery.[8] Attenuation or disappearance of a systolic murmur is not necessarily proof that no rheumatic lesion of the mitral valve has occurred.[7,11] One may conclude, therefore, that the appearance of a systolic murmur is usually considered evidence of carditis but not necessarily of valvulitis; a decrease in intensity or even complete disappearance fails to exclude a valvular lesion.

As far as the mitral diastolic murmurs are concerned, they should be carefully distinguished from loud diastolic sounds[8,12] considered to be "functional," e.g., caused by dilatation of the left ventricle because of carditis.[11,41] However, this interpretation is correct only if older attacks of rheumatic fever causing mitral stenosis can be excluded.

METHODS

Fifty-three patients of La Rabida Hospital were repeatedly studied. They were divided into three groups by clinical criteria.

Group I included twelve cases which were considered clinically to have *no rheumatic fever* or to be suffering from the *first attack of rheumatic*

* From the Division of Cardiology of the Chicago Medical School and La Rabida Jackson Park Sanitarium for Rheumatic Children. This study was made during the tenure of a Teaching Grant of the National Heart Institute, U.S.P.H.S. held by Dr. Luisada, and with the aid of a grant of the Chicago Heart Association.

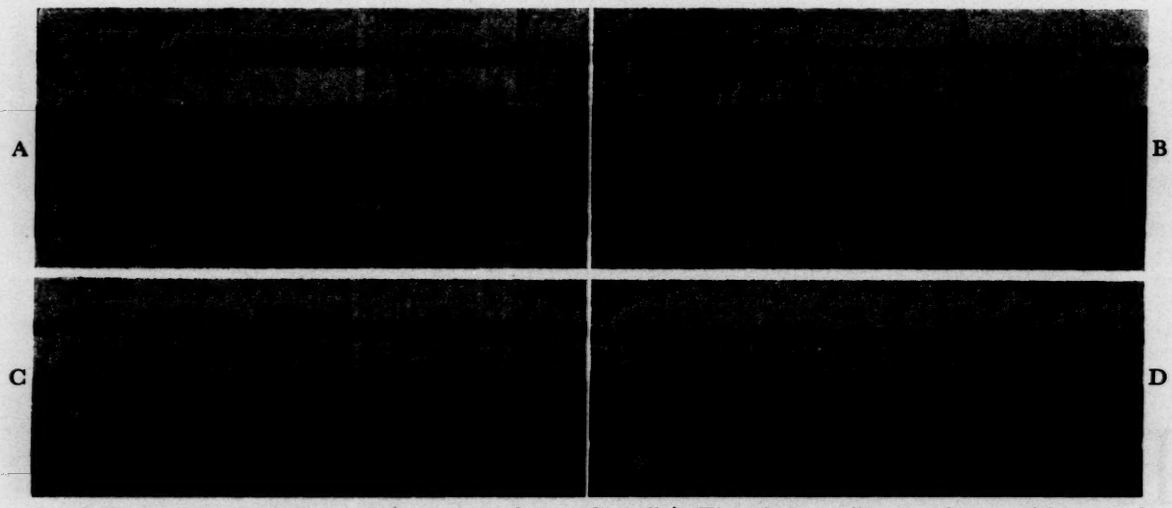

FIG. 1. Patient No. 3 of Group I (no cardiac lesion clinically). The phonocardiogram shows a faint apical systolic murmur (A) and a musical pulmonic murmur (B). The EKY was nearly normal at the first examination (C) and completely normal at the second (D). Conclusion: typical phonocardiographic picture of acute rheumatic fever without proven mitral regurgitation.

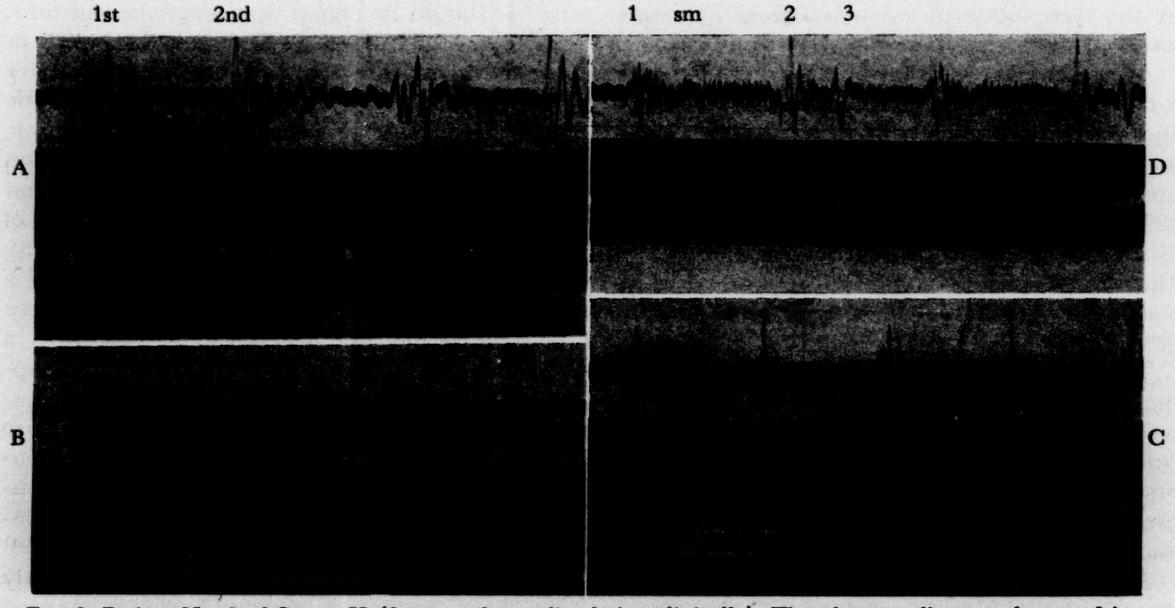

FIG. 2. Patient No. 2 of Group II (first attack; cardiac lesion clinically). The phonocardiogram shows a faint systolic murmur (A) which became louder four months later, after the end of the active stage (D). The EKY is within normal range at the first examination (B) and became typically abnormal at the second (C). The second complex is typical while the first is deformed through superimposition of respiratory waves. Conclusion: mitral regurgitation due to endocarditis.

fever but without cardiac involvement. This group was studied primarily as a control group. However, as shown subsequently, the findings were such that in some cases definite cardiac involvement could be established by the end of our study. Six of these patients in whom positive or doubtful results were found were studied a second time four to six months later. Another patient, also with positive findings, could not be traced at a later date. (Fig. 1.)

Group II included twenty-seven cases in whom the previous history was negative but the recent history and clinical data proved that they were suffering from *an initial attack of rheumatic fever, with some degree of cardiac involvement.* Fourteen of these cases had doubtful or negative findings at

the first examination and were submitted to a second examination within a period of four to six months. (Fig. 2.)

Group III included fourteen cases with a clear history of *recurrent attacks of rheumatic fever*. Actually, most of them had been admitted to La Rabida Hospital previously, so that older records were available. Ten patients with doubtful findings were checked again after four to six months. (Fig. 3.)

Technic. The phonocardiographic study was made by means of a Sanborn Stetho-Cardiette. The patients were in the supine position. All tracings were recorded first with a stethoscopic, then with a logarithmic microphone* at a film speed of 75 mm. per second. The murmurs were graded as faint, medium or loud.

The electrokymographic study† was made with a Sanborn electrokymograph connected with the electrocardiographic channel of the Stetho-Cardiette. Thus tracings of heart sounds were simultaneously recorded and used for timing purpose. Film speed of 75 mm. per second was used in all tracings.

The patients were studied in lying position, this being better tolerated than sitting by sick children and because it limited the possibility of movements. The slit was placed over the border of the left auricle at two different levels, first in the left oblique, then in the right oblique, according to the description of Luisada, Fleischner and Rappaport.[16] Thus four tracings were subsequently recorded, with the possibility of selecting those most appropriate and of discarding those apparently revealing artefacts or wrong location. It is to be noted that frequently one of the tracings revealed an "arterial pattern" due to recording of the pulsation of branches of the pulmonary artery. When recording in the left oblique position, the microphone was placed over the aortic area; when recording in the right oblique position, over the pulmonic area in order to avoid interference.

Phonocardiographic Pattern of Mitral Regurgitation. Patients with established mitral regurgitation present a typical apical murmur "in decrescendo." Occasional patients have an all systolic or even a late systolic murmur.[8,17] In addition, diastolic sounds are common, especially in children.[8,12] When diastole is short, their increased loudness may cause clinical impression of a diastolic rumble.

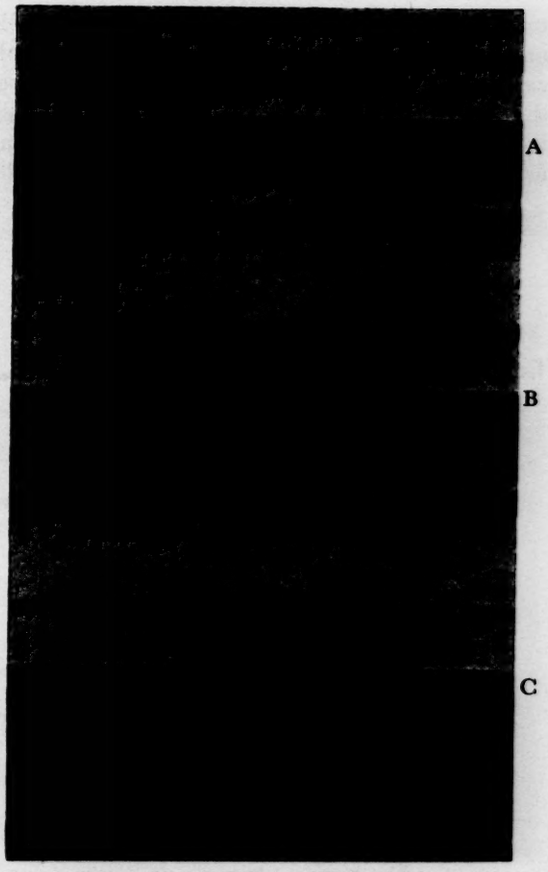

FIG. 3. Patient No. 6 of Group III (multiple attacks, cardiac lesions). The phonocardiogram shows an apical systolic murmur *in decrescendo* (A) and a loud, "diamond-shaped," pulmonic systolic murmur and an early diastolic murmur (B). The EKY has a typical plateau (C). Conclusion: mitral regurgitation due to endocarditis.

So-called "functional murmurs" have not been the object of special graphic studies. With the exception of murmurs caused by severe anemia, in general they are of poor amplitude and are limited to early systole.

Electrokymographic Pattern of Mitral Regurgitation. The electrokymograms (EKY) of the left auricle *in normal subjects* present a typical pattern consisting of: (1) A rather sharp negative wave in presystole caused by the contraction of the auricle. The peak is reached slightly before or at the time of the first vibrations of the first heart sound; (2) a return to the baseline during the

* The principles of stethoscopic and logarithmic phonocardiography were described by Rappaport and Sprague.[13] Further details can be found in the book of one of the authors.[17]

† The first practical electrokymograms were recorded by Henny and Boone.[14] Modifications of technic were described by one of the authors with Fleischner and Rappaport.[15]

tension period; (3) a rounded and occasionally deep negative wave during ventricular systole caused by traction exerted by the ventricle over the A-V floor, which is only partly compensated by venous flow into the auricle. The peak following this wave is reached from 0.04 to 0.05

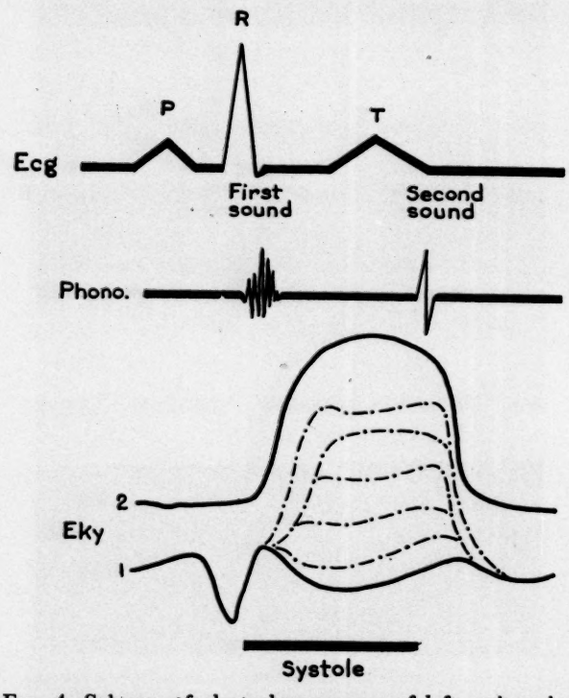

FIG. 4. Scheme of electrokymograms of left atrium in mitral lesions. Line 1: normal. Line 2: severe regurgitation and atrial fibrillation. Stippled lines: intermediate stages.

second after the main vibration of the second sound and coincides with the opening of the mitral valve. (Fig. 4.)

This normal pattern was originally described by Luisada, Fleischner and Rappaport[16] and has been confirmed by various authors.[18–28]

It has been known for a long time that mitral regurgitation causes a systolic distention of the left auricle. This is due to flow of blood under high pressure through the incompetent mitral valve into the left auricle. Tracings of left atrial pressure in animal[30] and man[31] are very conclusive in this respect. This systolic distention, if marked, can be recognized at fluoroscopy.[32] However, esophagocardiograms[33,34] or roentgenkymograms[35] are more accurate and revealing even if the regurgitation is moderate.

The EKY *pattern of mitral regurgitation*, described by Luisada and Fleischner,[36] was subsequently confirmed by Lian et al.,[18] Engstroem et al.,[20] Schwedel et al.,[24] Pannier et al.,[25] McKinnon and Friedman,[26] Soulié et al.[27] and Dack and Paley.[28] It consists of: (1) deeper and broader negative wave in presystole and (2) substitution of the negative systolic wave by a *positive plateau;* this has a rapid rise in early systole, a flat top

TABLE I

GROUP I: ACTIVE RHEUMATIC FEVER WITHOUT CARDIAC INVOLVEMENT OR NO RHEUMATIC FEVER

No.	Sex and Age	Duration of Illness (mo.)	Auscultatory Findings	X-ray	Ecg.	Phonocardiogram	Eky.
1	M, 13	?	neg.	neg.	neg.	ps	pos.
2	M, 6	3	ms, ps	neg.	neg.	ps	pos.
3	F, 8	1	ms, 3	neg.	neg.	ps, 3	neg.
4	F, 10	3	ms	neg.	neg.	ms	neg.
5	F, 7	10	neg.	neg.	neg.	neg.	neg.
6	F, 12	8	ms, ps	neg.	RAD	ms, ps	dbt.
7	M, 5	1	ms	neg.	neg.	ms	pos.
8	M, 11	?	ms	neg.	neg.	ms	neg.
9	F, 8	9	neg.	neg.	neg.	ms	neg.
10	M, 9	?	ms	neg.	neg.	ms	dbt.
11	F, 9	6	ps	neg.	neg.	ms, ps	pos.
12	M, 11	1	ps	neg.	neg.	ms, ps	pos.

ms = mitral systolic murmur; ps = pulmonic systolic murmur; 3 = third heart sound; dbt. = doubtful; RAD = right axis deviation.

and a rapid drop after the end of systole. Graphic differentiation between this plateau and the pulses of various arterial structures is usually not difficult and is based on the fact that these pulses have an oblique rise in early systole, a peak followed by a drop in late systole and a dicrotic wave in early diastole.[36]

RESULTS OF THE STUDY

Group I. No Rheumatic Fever, or First Attack without Clinical Recognition of Cardiac Involvement (12 Cases) (Table I). The phonocardiogram revealed a pulmonic systolic murmur in six cases, an apical systolic murmur in eight; only one case had no murmurs while three had both an apical and a pulmonic murmur.

The pulmonic murmur was faint in three cases, of medium intensity in two and loud in one. Of the four patients who were checked twice, only one still presented a definite pulmonic murmur at the second examination. The apical murmur was faint in seven cases, of medium intensity in one. Of six patients checked twice, four had an unchanged murmur at the second examination while two had no apical murmur.

The electrokymogram revealed a typical pattern of regurgitation in both oblique positions in one case; a typical pattern in only one oblique in three cases. Five cases had positive

findings in both the EKY and phonocardiographic tracings and also had positive auscultatory findings. Five cases had positive auscultatory and phonocardiographic findings but negative electrokymograms. The last two had practically no murmurs and had negative electrokymograms.

murmur at the first examination and only twelve at the second. An apical diastolic rumble was present in six cases. In two the diastolic rumble was not due to organic mitral stenosis because it disappeared between the first and second examination; in the others this conclusion could

TABLE II

GROUP II: ACTIVE RHEUMATIC FEVER WITH CARDIAC INVOLVEMENT AT FIRST ATTACK

No.	Sex and Age	Duration of Illness (mo.)	Auscultatory Findings	X-ray	Ecg.	Phono-cardiogram	Eky.
1	F, 14	10	ms, dr	5% oversize	1° A–V block	ms, dr	pos.
2	M, 12	9	ms, dr	enlarged	abn. P	ms, dr, 3	pos.
3	F, 11	6	ms, dr	sl. enlarged	RAD	ms, 3	pos.
4	M, 12	1	ms	sl. enlarged	A–V block	ms, 3	pos.
5	F, 12	4	ms	neg.	RAD	ms	dbt.
6	M, 10	2	ms	enlarged	A–V block	ms, 4	pos.
7	M, 12	3	ms	neg.	abn. P.	ms	neg.
8	M, 11	3	neg.	neg.	neg.	neg.	neg.
9	M, 12	4	ms, ps	prom. pulm.	RAD	ms, ps, dr	pos.
10	M, 8	1	ps	prom. pulm.	neg.	ms, ps, 3	dbt.
11	F, 12	3	ms, ps	neg.	abn. P	ms, ps, 3	pos.
12	F, 10	4	ps	prom. pulm.	RAD	ms, ps	pos.
13	F, 12	3	ms	neg.	neg.	ms, ps	pos.
14	F, 6	2	ms	neg.	RAD	ms, 3	pos.
15	F, 9	8	ms, dr	enlarged	sl. abn.	ms, dr	pos.
16	M, 14	3	ms	prom. pulm.	1° A–V block	ms, ps	pos.
17	F, 12	2	ms	prom. pulm.	abn. P	ms, ps	dbt.
18	F, 6	10	ms, 3	enlarged	LAD	ms, 3	pos.
19	M, 5	4	ms	15% oversize	neg.	ms	dbt.
20	F, 8	3	ms, dr, 3	60% oversize	1° A–V block	ms, dr	pos.
21	M, 8	5	ms, dr	enlarged	RAD	ms, pd	pos.
22	M, 6	1	neg.	prom. pulm.	1° A–V block	ms, pd, 3	pos.
23	F, 10	3	ms	neg.	neg.	ms	dbt.
24	M, 8	1	ms	neg.	neg.	ms	dbt.
25	F, 6	1	ms	neg.	1° A–V block	ms, dr	dbt.
26	M, 4	1	ps	neg.	neg.	ms	pos.
27	M, 6	1	ms	neg.	abn. P	ms, ps, 3	pos.

ms = mitral systolic murmur; dr = diastolic rumble; ps = pulmonic systolic murmur; pd = pulmonic diastolic murmur; 3 = third heart sound; 4 = fourth heart sound.

Group II. First Attack of Rheumatic Fever, with Cardiac Involvement (27 Cases) (Table II). The phonocardiogram revealed a pulmonic systolic murmur in eight cases, an apical systolic murmur in twenty-six; eight cases presented both types of murmurs.

The pulmonic murmur was faint in three cases, of medium intensity in the other five. Of fourteen cases checked twice, four had this type of murmur at the first examination but only three at the second. The apical or mid-precordial murmur was faint in fifteen cases, of medium intensity in nine, loud in two. Of fourteen cases checked twice, thirteen had this

not be reached with certainty. A basal diastolic murmur was present in two cases.

After examination of the various tracings recorded at different dates the electrokymogram was considered as revealing a pattern of regurgitation in eighteen cases, as negative in two, and as doubtful in the others.

Of the twenty-seven cases, then, twenty-six had a mitral systolic murmur and eighteen had typical EKY evidence of regurgitation. If the suspicious EKY tracings were included, only one case would have presented a mitral murmur and a normal EKY pattern.

Group III. Recurrent Attacks of Rheumatic

Fever (14 Cases) (Table III). The phonocardiogram revealed a pulmonic systolic murmur in only one case, an apical systolic murmur in all cases. There was an apical diastolic rumble in three cases, a basal diastolic murmur in four cases. All these murmurs were considered evidence of valvulitis. The apical systolic murmur often regular indicating a musical (or "seagull cry") type of murmur.[17] This murmur was less common in the group of patients who had suffered several attacks of rheumatic fever and, moreover, proved to decrease in amplitude in several cases repeatedly studied after an interval of three to six months. (Fig. 5 and Table IV.)

TABLE III

GROUP III: ACTIVE RHEUMATIC FEVER WITH CARDIAC INVOLVEMENT (RECURRENT)

No.	Sex and Age	Duration of Illness (yr.)	Auscultatory Findings	X-ray	Ecg.	Phonocardiogram	Eky.
1	M, 6	1	ms	sl. enlarged	neg.	ms, dr, ad	pos.
2	F, 6	2	ms	neg.	RAD	ms, dr, 3	pos.
3	M, 13	8	ms, dr	sl. enlarged	1° A–V block	ms	dbt.
4	F, 9	2	ms, 3	20% oversize	neg.	ms, 3	pos.
5	F, 13	6	ms, dr, ad	45% oversize	neg.	ms, 3	pos.
6	F, 12	7	ms, 3	enlarged	neg.	ms, 3	pos.
7	F, 12	5	ms	neg.	neg.	ms, 3	pos.
8	M, 12	2	ms, ad	30% oversize	LAD	ms, ad	pos.
9	M, 10	3	ms, dr, ad	enlarged	1° A–V block	ms, dr, ad	pos.
10	F, 15	5	ms	prom. pulm.	RAD	ms, ps	pos.
11	M, 13	4	ms	enlarged	RAD	ms	pos.
12	M, 11	3	ms	neg.	RAD	ms	pos.
13	M, 14	5	ms, ad	prom. pulm.	Sl. abn.	ms, ad	pos.
14	F, 8	4	ms	prom. pulm.	neg.	ms, 3	pos.

ms = systolic mitral murmur; dr = diastolic rumble; ps = pulmonic systolic murmur; ad = aortic diastolic murmur; 3 = third heart sound.

was faint in one case, of medium intensity in nine, loud in four.

The electrokymogram was considered as revealing a pattern of regurgitation in thirteen cases and doubtful in one. The clearly positive EKY findings were definitely in agreement with those of physical examination and of phonocardiography so that mitral regurgitation was evident in all cases.

COMMENTS

Our study was undertaken in order to evaluate, as far as possible, the damage caused by rheumatic fever during its early stages.

Phonocardiography revealed that in the first few months after onset of the first attack two types of murmurs can be recognized. One of them is a rather faint, high-pitched, early systolic murmur *in decrescendo*. The vibrations of this murmur are of low amplitude; however, with the progress of the disease they frequently become larger, indicating a louder murmur. The second is a louder, "diamond-shaped," pulmonic systolic murmur. Its vibrations are

Previous phonocardiographic experience has taught that an apical systolic murmur "in decrescendo" is typical of mitral regurgitation[17]

TABLE IV

Shape and Timing of the Murmurs	Group		
	1st	2nd	3rd
Pulmonic systolic murmur			
(a) musical, "diamond-shaped"	4	4	1
(b) faint, non-descript	2	4	0
Mitral systolic murmur,			
(a) early systolic "in decrescendo"	5	19	7
(b) mid-systolic, "diamond-shaped"	3	3	1
(c) all-systolic	0	4	6
Pulmonic early diastolic murmur	0	2	0
Aortic diastolic murmur "in decrescendo"	0	0	4

while a "diamond-shaped" pulmonic murmur is typical of pulmonic stenosis.[17] This, however, includes the murmurs caused by a "functional" mechanism, e.g., the apical systolic murmur

caused by dilatation of the mitral ring (relative mitral insufficiency) and the pulmonic systolic murmur caused by dilatation of the pulmonary artery (relative pulmonic stenosis).

In the early stages of rheumatic fever the following phenomena are likely to occur: (1) Dilatation of the mitral ring; (2) edema and infiltration of the papillary muscles; (3) edema of the mitral leaflets. All three may cause mitral regurgitation; the name "functional" has been applied to the murmurs caused by the first two, although improperly because the mitral regurgitation is associated with structural changes due to myocarditis; it should never be applied to the murmurs caused by the third because it consists of a structural change of the valvular cusps.

Another phenomenon may occur: (1) Dilatation of the pulmonary artery due to rheumatic arteritis, an extremely common lesion according to Kugel and Epstein (seventeen of twenty-four cases)[37] and Gross;[38] (2) dilatation of the pulmonary artery due to increased pressure, a secondary phenomenon which may be caused either by mitral regurgitation or left heart failure.

Phonocardiography easily permitted recognition of certain cases in which clinical auscultation had unduly emphasized the murmurs by proving that these were extremely faint. It also permitted exclusion of mitral stenosis by proving that a so-called apical diastolic murmur was actually a gallop or a rumble due to dilatation of the left ventricle.* On the other hand, phonocardiography was of no help in explaining the mechanism of production of these systolic murmurs. It has been proven by roentgenkymography and electrokymography that a systolic murmur may be present with a normal left atrial pattern[25,26] while patients with severe mitral regurgitation may have only a faint murmur or no murmur at all.[18,27,35,36] For this reason the electrokymographic patterns were studied with particular interest and their correlation with the other data was examined carefully. (Fig. 6.)

The normal pattern of left atrial contraction was described by Luisada, Fleischner and Rappaport[16] and was confirmed by several authors.[18–28] Only two discordant reports were published.[40,42] These can be attributed to: (1) tracings recorded with slow film speed; (2) nonrecording, poor recording or misinterpretation of the heart sounds tracing; (3) misinterpretation of the presystolic wave (the return of the tracing to the baseline after auricular contraction takes place *during the first heart sound;* the rise due to mitral regurgitation takes place much later, *during the ejection period);* and (4) technical errors. Special studies made by us in normal subjects confirmed once more the normal pattern of left atrial tracing.[29]

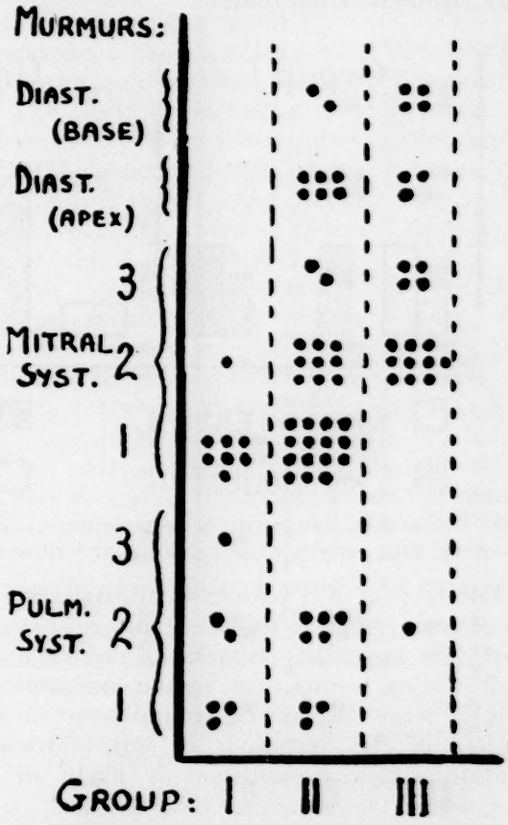

FIG. 5. Statistical distribution of the murmurs in the various groups. The decrease in diastolic apical murmurs and pulmonic systolic murmurs in Group III as compared with Group II indicates their functional nature.

Of twelve cases constituting our Group I, only five had an EKY pattern indicating regurgitation; of twenty-seven cases in the second group, eighteen had an EKY pattern indicating regurgitation; of fourteen cases of the third group, thirteen had a definite pattern of regurgitation. This shows that, while the EKY revealed regurgitation in only 41 per cent of the questionable cases, it revealed this type of dysfunction in 66 per cent of the patients at the

* A diastolic rumble caused by relative stenosis may be recognized at times because of the loudness and wide diffusion of the murmur; at other times because of its complete disappearance in subsequent examinations.[39]

time of their first attack, and in 92 per cent of those who had suffered repeated attacks.

Between the normal EKY pattern of the left auricle and that of clearly established regurgitation several intermediate steps can be recognized. (Fig. 4.) They indicate, in the authors' view, moderate regurgitation.

age and severe tachycardia may impair auricular function; auricular and ventricular damage, as well as mitral regurgitation, increase the amount of residual blood.

Therefore, the finding of an EKY pattern of regurgitation does not imply that this is caused by mitral valve damage. It simply means that

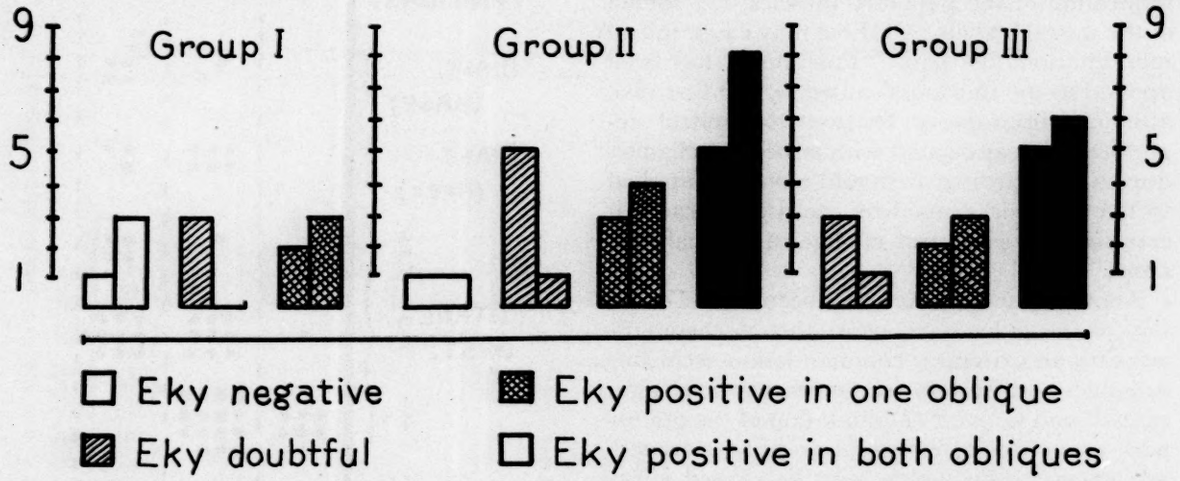

FIG. 6. Statistical distribution of electrokymographic patterns in the various groups. The gradually increasing percentage of the pattern revealing mitral regurgitation from Group I to Group III should be noted.

The finding of a pattern of regurgitation in an electrokymogram should be properly evaluated. The expansive pulsation of the left atrial wall during ventricular systole undoubtedly reveals some degree of transmission to the auricle of the variations of intraventricular pressure. This transmission is likely to be proportional to the following factors: (1) the amount of blood regurgitating; (2) the level of systolic ventricular pressure; (3) the distensibility of the left auricular wall (probably greater if this wall is damaged); (4) the amount of residual blood and level of atrial pressure during ventricular systole. Both severe auricular damage and severe tachycardia may impair auricular function; auricular and ventricular damage, as well as mitral regurgitation, increase the amount of residual blood.

Therefore, the finding of an EKY pattern of regurgitation does not imply that this is caused by mitral valve damage. It simply means that some kind of regurgitation is taking place, this being due either to myocarditis (auricular, papillary and ventricular damage favoring it) or endocarditis. On the other hand, the finding of a systolic murmur at the apex plus an EKY pattern of regurgitation indicates that the murmur is connected with the regurgitation, again without implying a mitral cusp lesion. (Table v.)

TABLE V
RESULTS OF THE GRAPHIC STUDY

Group	No. of Cases	Phonocardiographic Evidence of Murmurs				Electrokymogram of the Left Auricle		
		Pulmonary Systolic	Mitral Systolic	Apical Diastolic	Basal Diastolic	Typical	Suspicious	Normal
I	12	6	8	0	0	5	2	5
II	27	8	26	6	2	18	7	2
III	14	1	14	3	4	13	1	0

This interpretation is confirmed by the findings in subsequent examinations of patients of the first group. At the first examination a positive EKY pattern of regurgitation was found in two cases; a doubtful one, in three. At the

second examination one of the doubtful cases became positive, bringing the total to three; this was explained by the development of valvular lesions. On the other hand, the other two doubtful cases became normal, which was interpreted as healing of myocarditis.

Comparable findings were obtained in the second group, so that a definite correlation between graphic findings and clinical-roentgenologic improvement or aggravation was generally possible. The only exceptions were three of fourteen cases in whom clinical and auscultatory findings seemed to indicate healing while the EKY revealed a more severe regurgitation.

In the third group, two patients in whom the first study was made during the stage of acute carditis presented definite improvement in the EKY pattern at the second examination. This was interpreted as due to disappearance of the myocardial component of regurgitation, which left only that regurgitation caused by mitral lesions. All other cases were found to be unchanged at the second examination.

The coincidence of a loud, musical, "diamond-shaped," systolic murmur over the pulmonic area with an EKY pattern of mitral regurgitation probably indicates increased pressure in the left atrium, with secondary increase of pulmonic pressure stretching the pulmonary artery (so-called "relative" stenosis due to increased pressure). On the other hand, the appearance of a similar murmur in a patient with rheumatic fever who presents a normal EKY pattern of the left atrium could be explained by a rheumatic lesion of the pulmonary artery followed by its distention (again, "relative" stenosis due to local damage).

SUMMARY

A clinical and graphic study was made of fifty-three cases of rheumatic fever. The patients were studied by means of phonocardiograms and electrokymograms of the left auricle. Thirty patients were studied again after an interval of four to six months.

The patients were divided into three groups: (1) those with questionable rheumatic fever, or rheumatic fever without clinical cardiac damage; (2) those during the first attack of rheumatic fever, with clinical cardiac damage; and (3) those with recurrence of rheumatic fever.

The phonocardiographic findings are analyzed and discussed. Two types of murmurs were the most common in the early stages of rheumatic fever: (1) A soft, high-pitched, apical, systolic murmur "in decrescendo"; (2) a harsher, at times musical, "diamond-shaped" pulmonic murmur. The mechanism of production of these murmurs is discussed. In the later stages of the disease the apical murmur was often louder while the pulmonic was often less apparent. If healing of the lesions had occurred, both murmurs were less apparent or disappeared.

The electrokymogram in a high percentage of cases revealed a pattern due to transmission of intraventricular pressure to the left auricle on account of mitral regurgitation. The various myocardial and valvular elements causing this regurgitation are discussed.

The correlation between clinical, phonocardiographic and electrokymographic data proved that these graphic studies are of definite help not only in establishing the diagnosis but also in evaluating the severity of the regurgitation and of the cardiac murmurs. Evaluation of the part played by muscular and valvular factors in causing regurgitation was not possible after a single examination. On the other hand, repeated examinations during and after the active stage frequently permitted such evaluation.

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Quantitative Effects of Medical and Surgical Treatment of Mitral Stenosis on Exercise Tolerance*

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AFTER four years of clinical experience with mitral valve surgery the operative treatment is reported to be effective in relieving the symptoms and signs of pulmonary engorgement in from 50 to 80 per cent of the patients, with an over-all operative mortality of less than 15 per cent.[1–4] The left auricular pressure may be lowered by enlarging the mitral valve orifice.[5] The postoperative improvement has been associated with a decrease in intensity of the diastolic murmur at the apex of the heart.[6] Contrariwise, the absence of such changes, or the development of an apical systolic murmur of grade III intensity or greater, has been prognostic of a poor result.[6] The technic of venous catheterization of the heart and lungs has been employed to demonstrate a decrease in pulmonary arterial pressure and arteriolar resistance, together with a rise in cardiac output postoperatively.[7,8]

Although patients often report improvement in exercise tolerance or functional working capacity,[4] there has been no systematic study designed to quantitate either the degree or the rate of such improvement, and at the same time differentiate the effects of medical and surgical treatment of the heart disease. While there has been a tendency to urge operative treatment earlier in the natural history of mitral stenosis, a recent review indicated that "the mere presence of a mitral diastolic murmur without accompanying symptoms is not at this time sufficient reason to suggest surgery."[3] Hence there appears to be a need for an appropriate method of testing the severity of symptoms and disability in order to aid the clinical decision for or against surgery at any particular time in the course of mitral stenosis and its complications. Furthermore, since most of the operative mortality is associated with far advanced mitral heart disease, it would be helpful to know the minimal cardiac reserve that may be needed to withstand surgery.

In an earlier report a treadmill exercise tolerance test was proposed to meet the clinical need for quantitative data on the physiologic responses to ordinary types of exercise.[9] The stress was standardized with respect to the speed and grade of walking, and limited in duration by motivation of the patient, the intensity of symptoms or, more arbitrarily, to ten minutes' time. In the vast majority of patients tested motivation was appropriate and poor results were not due to this factor alone. The stress was proportional to body weight of each patient and represented a threefold increase in the oxygen requirement over the resting level. The test was sufficiently long to observe the optimal adaptations of respiration and circulation to meet these requirements. Salient responses to exercise could be expressed quantitatively in terms of a ratio designated the "physical fitness index" (PFI). The PFI was derived from the duration of exercise, the average exercise respiratory efficiency (the difference in volumes per cent between the

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concentrations of oxygen in inspired and expired air) and the sum of the heart rates for the first three minutes of recovery. The normal range of PFI values was 13 to 26, and abnormal values as low as 0.3 were recorded. The PFI varied inversely with the magnitude of the oxygen gradient between alveolar air and arterial blood during exercise, and directly with the arterial oxygen saturation.[9] Subsequent studies demonstrated that some of the functional changes of cardiorespiratory diseases could be simulated acutely in normal subjects by appropriate stresses of hypoxia or an increased work load.[10] It was apparent, therefore, that combining the physician's clinical knowledge of the patient with the patient's awareness of symptoms from this standardized exertion, supplemented by the changes in physical signs, physiologic measurements and precordial lead electrocardiograms during the test, should provide valuable information for the functional evaluation of the patient. This procedure represented the technics of physical and laboratory diagnosis, not at the usual resting level of metabolic activity alone, but in relation to a common form of physical work of moderate intensity, including observations of the recovery phase. Since the procedure was standardized, it would appear possible to compare performance in the same patient in relation to the natural history of his disease, to evaluate the effects of therapy or to compare the results of one patient with those of others. Finally, the test could be repeated innumerable times and the patient did not object to this procedure.

It is the purpose of this report to present the results of quantitative exercise tolerance tests in the first twenty patients with mitral stenosis who have been studied on several occasions, both preoperatively and from three to twelve months postoperatively.*

METHODS

The functional status of each patient was evaluated according to the criteria of the New York Heart Association.[11] Each patient was fluoroscoped with careful recording of the chamber enlargement, pulmonary engorgement and mitral valve calcification. Laboratory tests included electrocardiography together with phonocardiography (to establish the time relations of difficult murmurs), vital capacity, circulation time, venous pressure and arterial oxygen saturation (Van Slyke analyses) while breathing both air and oxygen. Cardiac catheterization was performed in the usual manner, except when refused by the patient's personal physician (for recent pulmonary emboli) or the patient (G. R.). The pulmonary arteriolar resistance and cross sectional area of the mitral valve orifice were estimated from the formulations of Gorlin.[12] The "pulmonary capillary" pressures were considered satisfactory when bright red blood, highly saturated with oxygen, could be withdrawn from the catheter wedged in the terminal pulmonary artery.

Quantitative exercise tolerance tests were done on a treadmill ergometer, to standardize the stress for walking at 1.7 miles per hour on a 10 per cent grade for ten minutes.[10] Observations were made of the heart rate, respiratory rate, blood pressure, precordial lead electrocardiogram and expired air oxygen tension serially at one-minute intervals. Symptoms were recorded. Changes in physical signs due to the exertion were noted, such as cyanosis, wheezes, râles, or accentuation of heart sounds, murmurs or gallop rhythm. The physical fitness index (PFI), previously described elsewhere, was employed to evaluate the patient's over-all physiologic performance.[10] Repeated tests were made before operation, as well as after, in order to evaluate the effects of medical and surgical treatment.

PATIENT MATERIAL

Clinical Data. The pertinent clinical data on twenty patients with rheumatic heart disease evaluated with respect to mitral valve surgery are presented in Table 1. There were thirteen women and seven men ranging in age from nineteen to fifty years. Fifteen had a history of symptoms or signs of pulmonary congestion; eight, hemoptysis; four, emboli (pulmonary in F. B. and M. F.); and seventeen, tachycardia and/or palpitation. They had had these symptoms from less than one to over thirty years. Six of these patients presented evidence of moderate cardiac enlargement involving chiefly the left auricle, right ventricle and the right auricle; twelve others had slight enlargement of the heart. None had any marked and clearly

* The authors are indebted to Drs. S. F. Aronson, W. C. Bridges, R. L. King, J. H. Lehman, D. L. Sparkman and W. E. Watts, who referred patients for these studies, and to Drs. K. Alvin Merendino, Fred Jarvis and Dean K. Crystal for permitting an independent evaluation of their operative results.

recognizable enlargement of the left ventricle by fluoroscopy or left axis deviation by electrocardiogram. Thirteen patients, however, exhibited normal axis or intermediate position of the electric field of the heart. Three had a systolic murmur at the apex of moderate intensity (grade III, using a scale of I to VI) and four others of slight intensity (grade II). A grade III early diastolic murmur at the base and along the left sternal border was apparent in four patients and six others had a variable or slight murmur of this type. One-half of the patients had auricular fibrillation but only one of these was successfully converted to normal sinus rhythm with quinidine preoperatively. Each patient had auscultatory evidence of mitral stenosis but the timing and intensity of the diastolic murmurs varied widely. The functional and therapeutic classification of fourteen patients was IIIC. Each of these patients had disability of progressive severity. There were two patients in each of the other categories: IA, IIB and IVD. None of these patients had evidence of active rheumatic carditis or subacute bacterial endocarditis.

TABLE I

CLINICAL DATA IN PATIENTS WITH MITRAL STENOSIS

Patient	Age	Sex	History of Pulmonary Congestion	Previous Hemoptysis or Emboli		Right Ventricular Failure	Tachycardia or Palpitation	Duration of Symptoms (yr.)	Cardiomegaly	Apical Systolic Murmur	Early Diastolic Murmur	Rhythm	ECG Findings*	Clinical Classification
M. R.	44	F	+			+	+	31	++			AF	R	IIIC
F. B.	26	F	+	H	E†	+	+	12	++	++	+++	AF	N+	IIID
E. D.	44	M	+				+	1	+++			NSR	P, R+	IIIC
C. B.	26	M		H		+	+	9	+++	+++		NSR	P, R+	IIIC
J. D.	50	F	+				+	30	+++			AF	N+	IIIC
J. B.	40	F					+	13	+	+	++	NSR	N	IIIC
P. D.	32	F	+	H		+	+	14	++		+	NSR	P, N	IIIC
H. C.	39	F	+		E	+	+	3	++	+++	+	AF	R	IVD
L. L.	38	M	+			+	+	5	+++		+	AF	N+	IIIC
G. S.	38	F	+				+	10	+++	++	+	NSR	P, R+	IIIC
M. F.	35	M		H	E†			<1				AF	N+	IA
P. S.	43	M	+	H		+	+	2	++	++	+++	NSR	P, N	IVD
E. B.	39	M	+				+	6	++			AF	R	IIB
T. J.	50	F			E	+	+	14	++	+++	+	AF	N+	IIB
F. C.	45	F	+				+	3	++	+		AF	N	IIIC
G. R.	19	F	+	H		+		1	+			NSR	N	IA
B. K.	38	F	+	H			+	16	++		+++	NSR	P, N	IIIC
W. S.	41	M	+	H				11	+			NSR	P, R+	IIIC
H. K.	46	F					+	14	++	++		NSR	N	IIIC
C. McC.	47	F	+			+	+	15	+++		+++	AF	N	IIIC
Comments:														
	13	F	15+	8H		10+	17+	<1–31	6+++	3+++	4+++	10AF	7P, 13N	2IA
	7	M	75%		4E	50%	85%		10++ 3+	4++	5+ 1++	10NSR	7R, 9+	2IIB 13IIIC 2IVD

* P = Prominent P waves (auricular hypertrophy); R = right axis deviation; N = normal axis; + = right heart strain or hypertrophy.
† The emboli were pulmonary.

Indications for Mitral Valve Surgery. Eighteen patients were submitted to operation because of symptoms and signs of pulmonary engorgement and varying degrees of impaired working capacity due to mitral stenosis. Two others classified as IA were submitted to mitral commissurotomy for the following reasons: A history of congestive heart failure during previous pregnancies but no functional impairment between pregnancies (G. R.); and for ablation of the auricular appendage as prophylaxis against future arterial emboli in the presence of persistent auricular fibrillation (M. F.).

Catheterization Data. The femoral arterial oxygen saturation varied from 81 to 96 per cent in seventeen of these patients; it was 95 per cent or higher in only three. (Table II.) It increased to a range of 87 to 100 per cent while these patients breathed oxygen, and nine then had values of 95 per cent or more. The cardiac index ranged from 1.46 to 3.73 L./M²/minute. Eight of the seventeen patients had values of less than 2.5. The mean resting pulmonary arterial pressures ranged from 23 to 80 mm. Hg, whereas the mean "pulmonary capillary" pressures were increased to a range of 18 to 45 mm. Hg. Only one patient, E. B., exhibited large "V waves," thought to be indicative of mitral insufficiency.[13] He also had auscultatory and palpatory evi-

dence of mitral insufficiency. (Table I.) The mitral valve orifice was estimated to be reduced to a range of 0.6–1.2 cm^2. Pulmonary arteriolar resistance varied rather widely from low normal values of 47 to abnormally high values of 915 dynes sec. $cm.^{-5}$.

patients had finger-fracture of both the anterolateral and posteromedial commissures. In two patients with fibrous valves the operator was unable to perform more than a manual dilatation of the orifice. In another patient, F. B., the valve was subjected to a posterior valvulotomy.

TABLE II

CARDIAC CATHETERIZATION AND OPERATIVE DATA

Patient	Arterial O_2 Sat. Per cent		Cardiac Index (L./M^2/m.)	Stroke Volume (ml.)	PA Mean Pressure (mm. Hg)	"PC" Mean Pres. (mm. Hg)	Mitral Valve Orifice (cm^2)	Pulmonary Arteriolar Resistance (Dynes sec. $cm.^{-5}$)	Auricular Pathology*	Regurgitant Jet		Valve Type*	LA Mean Pressure mm. Hg		Operative Procedure (FF)†
	Air	O_2								B	A		B	A	
M. R.	90	93	2.52	54	52	35	1.1	298	ET	−	−	Calc.	32	17	+
F. B.	..	..	....	..	..	..	...	...	E	−	−	Memb.	35	26	PV
E. D.	96	97	1.46	43	36	29	.7	186	...	−	−	.....	..	..	.....
C. B.	87	98	3.41	79	49	28V	1.2	271	E	++	+	Calc.	..	..	++
J. D.	90	95	2.64	49	24	21	.9	60	E	−	−	Calc.	..	..	++
J. B.	83	87	2.23	36	58	..	...	...	E	−	−	Calc.	11	..	+
P. D.	93	100	3.02	56	50	45	.7	85	...	−	−	Calc.	..	..	+
H. C.	89	97	1.55	21	62	31	.6	795	...	−	−	Memb.	20	14	+
L. L.	81	93	2.30	61	58	27	.9	610	...	+	−	Calc.	..	..	PV
G. S.	88	91	3.34	64	..	..	...	...	E	−	−	.....	..	..	++
M. F.	..	..	....	..	..	..	...	...	T	−	−	Memb.	12	10	Dil
P. S.	95	86	3.73	63	55	38	.8	269	...	+	−	Calc.	..	..	.....
E. B.	93	96	2.03	60	25	18	.8	155	...	−	−	.....	..	..	.....
T. J.	91	90	3.44	60	31	25	1.1	94	...	±	±	Fib.	..	..	++
F. C.	85	93	2.31	26	36	..	...	...	ET	−	−	Calc.	20	16	+
G. R.	..	..	....	..	..	..	...	...	...	−	+	Calc.	16	16	+
B. K.	91	96	2.98	46	80	29	1.1	915	...	−	−	Memb.	..	..	Dil.
W. S.	86	92	2.78	56	42	26	.9	277	...	−	−	Calc.	..	..	+
H. K.	96	99	2.08	43	23	21	.9	47	E	−	−	Calc.	24	..	+
C. McC.	92	96	2.13	49	56	25	.7	668	ET	+	−	Fib.	..	..	+
Comments:															
Air 81–96			1.46 to 3.73	21 to 79	23 to 80	18 to 45	.6 to 1.2	47 to 915	9E 4T	3+ 15−	1+ 17−	11 C. 4 M. 2 F.	11 to 35	12 to 26	9+ 4++ 2PV 2 Dil.
O_2 86–100															

V = Prominent V wave in "PC" pressure record

* E = Enlarged left atrium and appendage; T = thrombus in atrium or appendage; Calc. = calcification of the mitral valve; Memb. = membranous mitral valve; Fib. = fibrous mitral valve; PA = pulmonary artery; LA = left auricle.

† FF = Finger fracture
+ = Anterolateral commissure
++ = Anterolateral and posteromedial commissure
PV = Posterior valvulotomy
Dil. = Dilatation of orifice
B, A = Before or after

Operative Findings. The pathologic conditions encountered in the left auricle at operation varied considerably. (Table II.) Nine patients presented auricular enlargement, usually involving the appendage and four had mural thrombi but no peripheral emboli occurred during surgery. Over one-half of the patients had markedly calcified mitral valves whereas in the remainder the valves were either fibrous or thickened elastic membranous leaflets with a rubbery consistency, or a combination of both. Finger-fracture of the anterolateral commissure was accomplished in most instances. Three

Postoperative Complications. The postoperative complications encountered within the first two weeks included atelectasis, pneumonia, transient pulmonary edema, hyponatremia, hypochloremia, peripheral emboli and paroxysmal auricular fibrillation. One patient, G. S., had a pleural effusion that persisted for several months.

Postoperative Changes in Physical Findings. The clinical effects of mitral valve surgery were related chiefly to the improved functional status which will be described subsequently. There was no reduction in heart size in any patient. Of nine patients who had an apical

systolic murmur initially, there was an increase in intensity of the murmur in only one patient, diminution or disappearance of the murmur in three. The diastolic murmurs of mitral stenosis disappeared in only two patients, J. B. and G. R., but decreased in intensity in several others. An early diastolic murmur at the base and along the left sternal border disappeared in four patients but increased in intensity in two other patients. In no instance did any patient spontaneously convert auricular fibrillation to normal sinus rhythm but this arrhythmia was converted by quinidine therapy in four patients. Two of these patients had arrhythmia preoperatively and two had acute paroxysms after the operation. There were no other significant changes in the resting electrocardiogram attributed to mitral valve surgery.

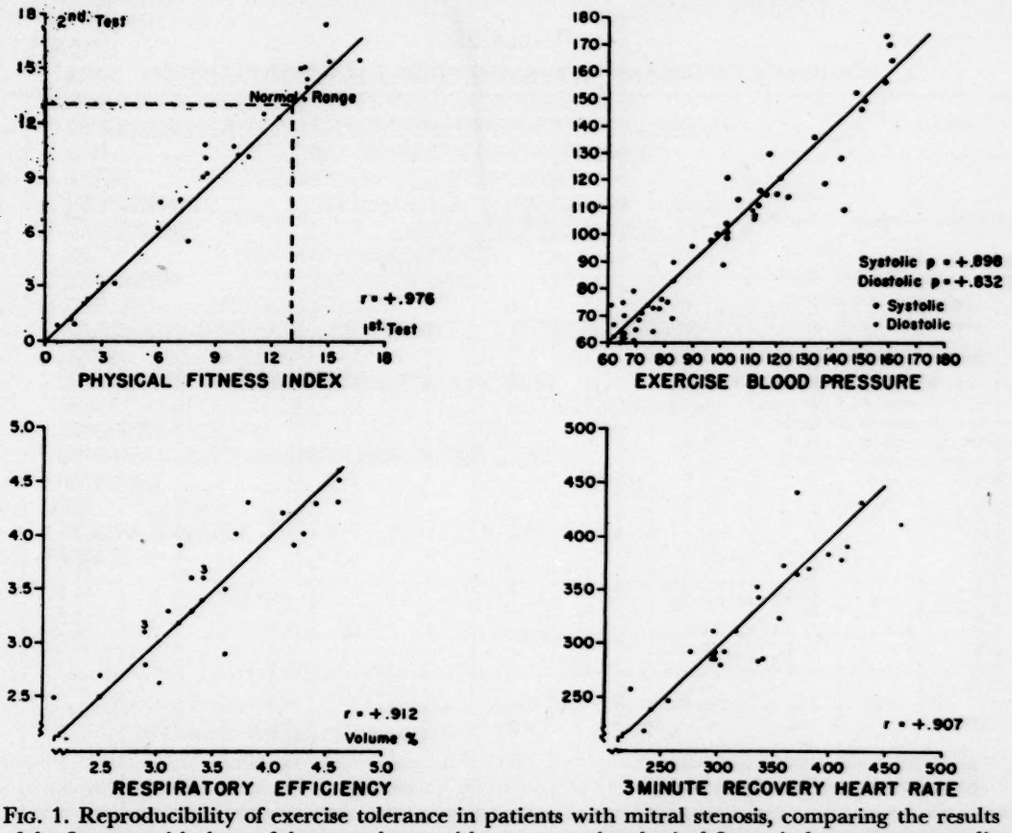

FIG. 1. Reproducibility of exercise tolerance in patients with mitral stenosis, comparing the results of the first test with those of the second test, with respect to the physical fitness index, average systolic and diastolic pressures during exercise, average exercise respiratory efficiency and the total number of heart beats during the first three minutes of recovery. The coefficients of correlation are indicated.

RESULTS OF EXERCISE TOLERANCE TESTS

Reproducibility of Exercise Tolerance. In order to ascertain the reproducibility of the standardized exercise tolerance test in patients with mitral stenosis, twenty-seven comparisons were made in twenty-one patients during periods when there were no clinically apparent changes in the functional status. The difference in time between the two tests varied from 0 to 24 days, with a median of 2 and an average of 5.8 days. The distribution of results with respect to the physical fitness index, systolic and diastolic blood pressure, and respiratory efficiency during exercise, together with the total heart beats for three minutes of recovery, are shown in Figure 1.

The coefficients of correlation between these pairs of data are as follows:

Measurement	Mean (Range)	Coefficient of Correlation*
Duration of exercise, minutes	7.8–7.7 (0.75–10.0)	+0.980 ± .001
Physical fitness index	8.9–9.1 (0.6 –16.6)	+0.976 ± .001
Respiratory efficiency, exercise	3.5–3.5 (2.1 – 4.6)	+0.912 ± .003
Recovery pulse, 3 min., total	333–323 (223 – 463)	+0.907 ± .003
Systolic blood pressure, exercise	126–126 (97– 173)	+0.898 ± .003
Respiratory rate, exercise	28– 28 (12 – 40)	+0.852 ± .005
Diastolic blood pressure, exercise	77– 75 (60 – 112)	+0.832 ± .006

* The probability that these correlations are due to chance is <.001 in all instances.

Effects of Preoperative Medical Treatment. A satisfactory correlation was obtained generally between the history of exertional dyspnea and fatigue and the actual awareness of these symptoms during the standardized exercise test. (Table III.) Only one patient, M. F., who had a 1 gm. of sodium chloride) and the use of diuretics as indicated. As a result of this regimen the PFI was increased to a range of 2.2 to 14.6, with an average of 7.6 in eighteen patients. (Fig. 2.) The individual changes varied widely. The PFI was at least 0.3 lower in two patients and showed a

TABLE III

EFFECTS OF PREOPERATIVE TREATMENT ON EXERCISE TOLERANCE

Patient	History of:		Initial Test			Preoperative Treatment Rx:			Final Preoperative Test			Change in PFI
	Dyspnea	Fatigue	Symptoms	Endurance (min.)	PFI	Rest, Digitalis, Low Salt	Duration of Rest (wk.)	Other Rx	Symptoms	Endurance (min.)	PFI	
M. R.	+++	+	D, LP	1.5	1.7	+	2	..	S, D	1.5	2.7	+1.0
F. B.	+++	+	D	2.5	2.5	+	5	Q	D, F	2.5	2.2	−0.3
E. D.	++++	+	D	2.8	4.6	+	1	..	D	3.0	4.7	+0.1
C. B.	++	++	D	1.0	1.2	+	4	..	D, Pa	6.0	6.9	+5.7
J. D.	+++	+	D, Pa	1.5	1.8	+	8	..	D, F	4.2	6.2	+4.4
J. B.	++	++	D	6.2	3.3	+	4	..	P	10.0	7.6	+4.3
P. D.	++	+++	D, F	5.3	4.0	+	4	..	D	10.0	10.2	+6.2
H. C.	++	++	D, F	0.8	0.6	+	6	..	D	4.5	5.2	+4.6
L. L.	+++	++++	D, F	4.1	3.4	+	4	..	D, F	7.0	7.7	+4.3
G. S.	+++	+++	D	1.8	1.3	*	8	..	D	4.8	4.4	+3.1
M. F.	.....	.....	.....	10.0	11.3	+	3	..	.....	10.0	14.6	+3.3
P. S.	+++	.....	D, F	2.3	1.5	+	10	T	D, F	2.5	3.0	+1.5
E. B.	++	.....	F	10.0	11.3	+	1	..	D	10.0	10.9	−0.4
T. J.	++	.....	F, Fr	0.8	1.2	+	4	..	F	10.0	14.2	+13.0
F. C.	++	++	F, S	6.5	6.1	+	8	..	F	10.0	12.3	+6.2
G. R.†	+++	.....	D, F	10.0	12.5	+	3	..	.....	10.0	13.9	+1.4
B. K.	++++	.....	D	3.5	2.9	+	6	..	D	10.0	7.8	+4.9
W. S.	+++	++	D, LP	1.1	0.8	+	8	Q	D, F	3.5	2.2	+1.4
H. K.	++	++	D, F	5.0	5.5	+	6	..	D, F	8.5	13.5	+8.0
C. McC.	++++	+++	F, Pa	1.5	1.1	+	3	..	D, F, Pa	2.5	2.7	+1.6
Comments:												
	19D	14F	15D 2Pa 9F 2LP 1S	0.8 to 10.0	0.6 to 12.5	Range Mean	1–10 4.9		15D 2Pa 9F 1P 1S	1.5 to 10.0 6.6	2.2 to 14.6 7.6	−.4 to +13 +3.7

* Unable to tolerate any preparation of digitalis or squill.

† Hospitalized 4 months earlier because of pregnancy and congestive heart failure.

D = Dyspnea; F = Fatigue; S = Syncope; Fr = Fright; Pa = Palpitations; P = Pain in chest; LP = Pain in legs; Q = Quinidine; T = Thoracentesis

class IA status, did not have these symptoms under any of these circumstances. No patient with a history of fatigue was able to walk for longer than 6.5 minutes or had a physical fitness index of over 6.1. The initial PFI was subnormal in all twenty patients; it varied from 0.6 to 12.5. The average score was 4.0. There were certain patients (E. B. and G. R.), however, who did not have a history of fatigue even though they experienced it during the test, without necessarily impairing their endurance.

Each patient was prepared for the operative procedure by a period of medical treatment that lasted from one to ten weeks; the average time was 4.9 weeks. This treatment consisted of bed rest, optimal digitalization, low salt diet (usually maximum rise of thirteen in another patient, T. J. In the latter instance much of the apparent improvement was due to the falsely low value of 1.2 obtained initially. Her complaint of fatigue with the initial test, which lasted only 0.8 minute, stood in marked contrast to the absence of a history of fatigue with ordinary physical activity. She was the only patient in this series who exhibited poor performance because of anxiety and inappropriate motivation. This woman later admitted that her poor performance was due to her fright about the testing procedure. Yet, at the time of cardiac catheterization the resting pulmonary capillary pressure was elevated to 25 mm. Hg, and the mitral valve orifice was estimated to be 1.1 cm^2

in cross sectional area. Twelve of the other nineteen patients showed appreciable increments in the duration of time that they could walk on the treadmill after a period of medical treatment, including bedrest. (Table III.)

Comment: Repeated exercise tolerance tests were of value pre-operatively to confirm the subjective evaluation of the severity of the disability due to mitral stenosis, to evaluate the effects of digitalis and other treatment on myocardial reserve in the presence of increased resistance to mitral valve flow, and to reassure the operator that the patient had sufficient reserve to withstand the stresses of general anesthesia, thoracotomy and cardiotomy. In addition, this procedure provided a baseline for the evaluation of the benefits of surgery separate from the effects of medical treatment.

Somewhat arbitrarily, no patient was recommended for operation unless the PFI exceeded 2.0. In some instances this appeared to delay the operation by a few weeks. Yet the lack of any operative mortality due to a poor selection of patients to date, and the relatively rapid postoperative convalescence in patients who waited longer, justified this policy.

Effects of Mitral Valve Surgery. The distribution of patients according to the functional and therapeutic classifications of the New York Heart Association before and after optimal

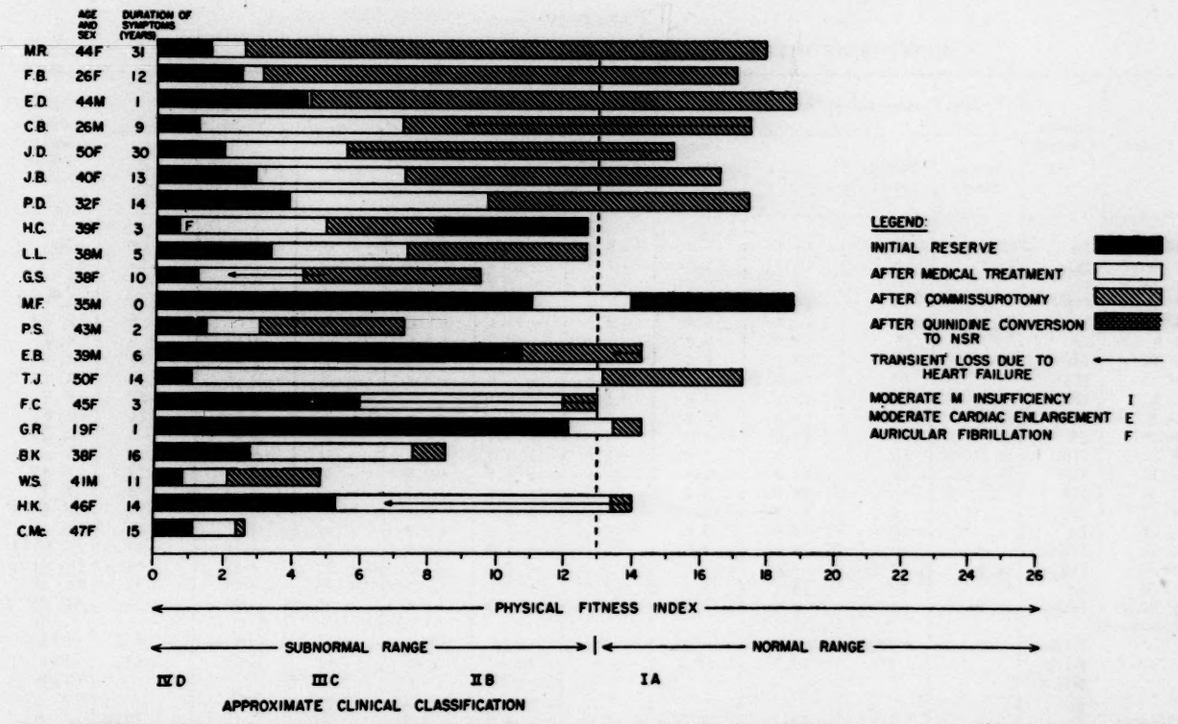

FIG. 2. Effects of mitral commissurotomy on cardiac reserve. Individual variations in exercise tolerance, expressed in terms of the physical fitness index, to indicate the relative effects of medical treatment preoperatively and mitral commissurotomy. In addition the successful conversion of auricular fibrillation (F) to normal sinus rhythm with quinidine, or the subsequent deterioration of functional capacity due to heart failure (←) in certain patients are shown. The presence of moderate mitral insufficiency (I) or moderate cardiac enlargement (E) are also indicated.

improvement from mitral valve surgery was as follows:

Classification	Preoperative	Postoperative
IA	2	7
IIB	2	9
IIIC	14	4
IVD	2	0
	20	20

The results of the best postoperative exercise tolerance test are compared with those of the final preoperative performance in Table IV and Figure 2. These follow-up data were obtained from 1.5 to 9 months after the operation. Only

seven patients still had dyspnea and three still had fatigue during the standardized exercise test. Yet, at the same time, there were thirteen patients who were rated clinically as IIB or IIIC. (Table IV.) There was appreciable improvement in endurance in four of these individuals, no change in one and a decrease in two. Only one patient failed to exhibit any objective improvement in terms of an increase in PFI. This was C. McC., a forty-seven year-old white woman with symptoms for fifteen years, moderate cardiac enlargement, auricular fibrillation, early diastolic murmur and balanced axis in the electrocardiogram. A densely fibrous mitral valve with a small slit and faint regurgitant jet was felt at operation. The anterolateral commissure was finger-fractured. Part of the failure to demonstrate any improvement may have been due to the patient's disregard of postoperative medical management in regard to digitalis.

TABLE IV

EFFECTS OF MITRAL VALVE SURGERY ON EXERCISE TOLERANCE

Patient	Postop. Clinical Class	Best Postoperative Test			Elapsed Time (mo.)	Comparison with Final Preoperative Test Changes						Post-operative EGG*
		Symptoms	Endurance	PFI		Endurance	PFI	R.E.	H.R.	Systolic Ex.	B.P. Rec.	
M. R.	IA	.....	10	18.3	7.0	+8.5	+15.6	+0.9	− 24	+23	+28	AF
F. B.	IIB	D	10	17.7	4.0	+7.5	+15.5	+1.5	−104	+ 9	−12	SR, T
E. D.	IA	.....	10	19.7	2.0	+7.0	+15.0	+0.9	− 9	+13	−12	SR
C. B.	IIB	.....	10	18.2	5.0	+4.0	+11.3	+1.3	− 77	− 2	−28	SR, VPS
J. D.	IIIC	D, F	7.5	16.3	5.0	+3.3	+10.1	+1.0	− 23	+15	+ 8	AF, ST
J. B.	IA	.....	10	17.3	9.0	.....	+ 9.7	+1.6	−104	+20	+ 9	SR, T
P. D.	IA	.....	10	18.3	4.5	.....	+ 8.1	+1.1	− 76	+29	+13	SR, T
H. C.	IIB	.....	10	13.0	5.0	+5.5	+ 7.8	+0.5	− 1	− 4	−11	SR, ST-T
L. L.	IIB	.....	10	13.2	3.0	+3.0	+ 5.5	.....	− 77	+27	+82	AF
G. S.	IIIC	D, F	10	9.8	7.5	+5.2	+ 5.4	+0.5	+ 26	+12	+16	SR, ST
M. F.	IA	.....	10	19.6	7.0	.....	+ 5.0	+1.5	− 13	+24	+ 1	SR, ST
P. S.	IIIC	D, F, Pa	10	7.5	2.0	+5.8	+ 4.5	−0.2	− 47	− 1	....	SR
E. B.	IIB	D	10	14.9	1.5	.....	+ 4.0	+0.9	− 23	+ 6	−12	AF, ST
T. J.	IIB	.....	10	18.0	5.0	.....	+ 3.8	+1.2	− 9	+ 3	+ 8	AF, T
F. C.	IIB	.....	10	17.3	10.0	.....	+ 5.0	+0.5	− 67	+10	+30	AF, ST-T
G. R.	IA	.....	10	14.9	3.0	.....	+ 1.0	+0.9	+ 49	+ 7	−10	SR
B. K.	IIB	.....	10	8.8	3.0	.....	+ 1.0	+0.3	− 27	+24	+22	SR, ST-T
W. S.	IIB	D, F	7.25	6.0	2.5	−0.7	+ 3.8	+1.2	+ 27	+31	+28	SR, ST-T
H. K.	IA	.....	10	14.1	5.0	+1.5	+ 0.6	.....	+ 38	+18	+24	SR, ST
C. McC.	IIIC	D, Pa	2.25	2.5	3.0	− .25	− 0.2	+1.1	− 47	−10	+28	AF, ST, T
Comments:												
	7-1A		2.25 to	2.5 to	1.5 to	−.7 to	−2 to	−.2 to	−104 to	−10 to	−28 to	AF7
	9-IIB		10	19.7	10.0	8.5	15.6	1.6	+49	+29	+82	VPS1
	4-IIIC											ST10
												T9
Average:			9.3	14.2	4.7	2.5	6.6	8.4	− 29	12.7	10.6	

* AF = Auricular fibrillation; SR = normal sinus rhythm; ST = depressed ST segment; T = inverted or depressed T waves.

Nineteen patients showed an increase in the PFI ranging from 0.6 to 15.6. (Fig. 2.) The average increment was 6.6.There was no apparent correlation between the duration of symptoms prior to surgery and the degree of postoperative improvement. The greatest improvement in the physical fitness index occurred in M. R. who had had symptoms for thirty-one years. (Because her reserve was so poor, the operation was postponed when the anesthetist discovered a fall in systolic pressure to 76 mm. Hg, together with a very slow heart rate due to preoperative medications. Her preoperative PFI was 2.7. With more judicious choice of drugs preoperatively she was able to undergo the operation a few days later.)

The rate of improvement following mitral valve surgery was not uniform. Approximately one-half of the patients showed increase exercise tolerance within the first three months after the operation. (Fig. 3A.) The remaining one-half of the patients either showed no improvement or were worse for several weeks and then gradually improved. (Fig. 3B.) One patient, G. S., required eight months to increase her exercise tolerance; this patient was never digitalized due to intolerance of various digitalis preparations and squill.

The changes in various physiologic parameters associated with the improvement in exercise tolerance in a single patient (P. D.) after

preoperative medical treatment, as well as mitral valve surgery, are shown in Figure 4. Following a period of bedrest and optimal regulation of diet, digitalis and diuretics there was an increase in endurance so that she was able to walk for ten minutes. The tachycardia, tachypnea and failure to increase either the systolic pressure or the respiratory efficiency during the exertion were unchanged, and the abnormal rebound in the systolic pressure in early recovery still occurred. After an anterolateral commissurotomy, however, all abnormalities except the rebound in systolic pressure in recovery had disappeared. The PFI increased from an initial value of 4.0 to a preoperative value of 10.2, and a postoperative value of 17.6. Since then all medical treatment has been discontinued.

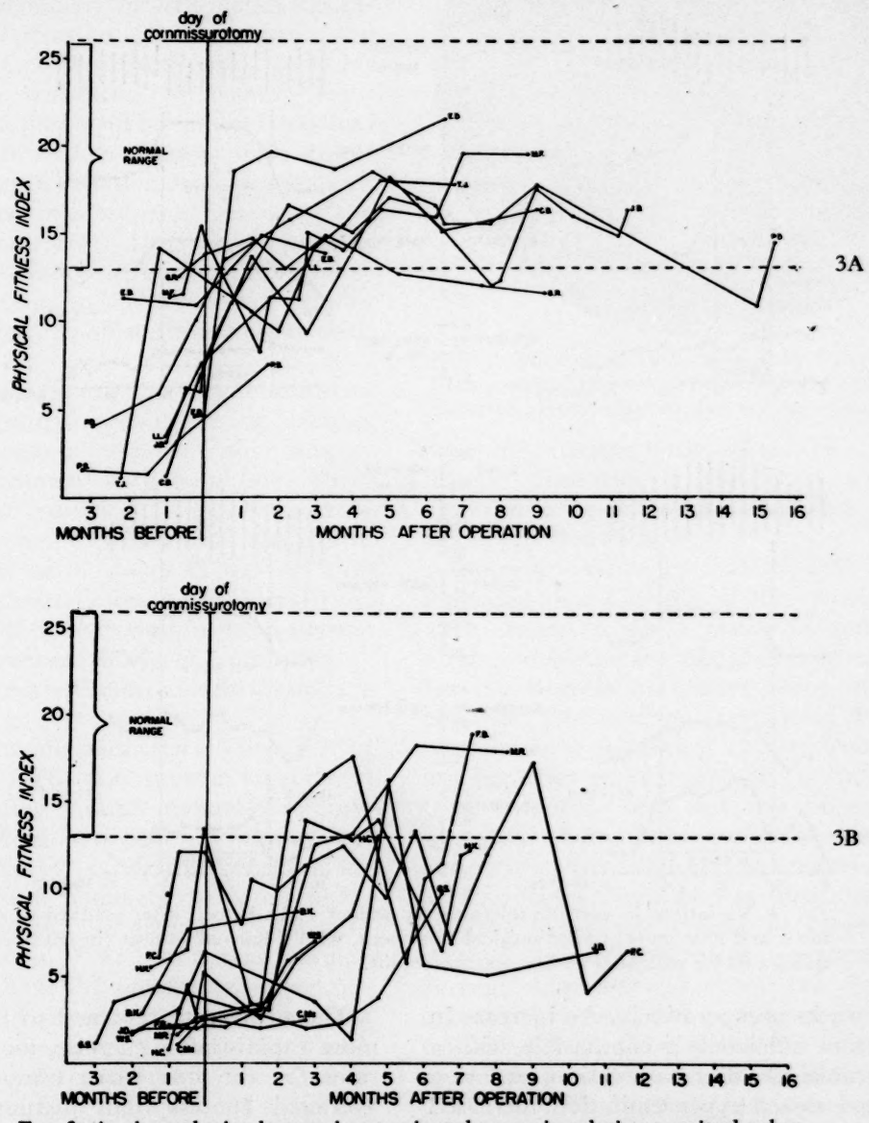

FIG. 3. A, chronologic changes in exercise tolerance in relation to mitral valve surgery. Note the general trend for relatively early and substantial improvement in the physical fitness index in these patients. B, note the tendency toward delayed and less significant improvement in the physical fitness index, together with the tendency for decreases in performance in subsequent months in the remaining patients. In some patients, such as F. C., this occurred on more than one occasion.

In addition to the increased endurance to the standardized exercise tolerance test there were

also changes in other physiologic measurements. The respiratory efficiency during exercise increased by a range of 0.3 to 1.6 volumes per cent in seventeen patients. There was no change in two others, and a negligible decrease in a third patient. The latter had had a left pleural effusion

endurance together with a rise in respiratory efficiency. All the others exhibited the same or increased endurance together with improved respiratory efficiency. The average change in respiratory efficiency for the entire group was +0.9 volumes per cent.

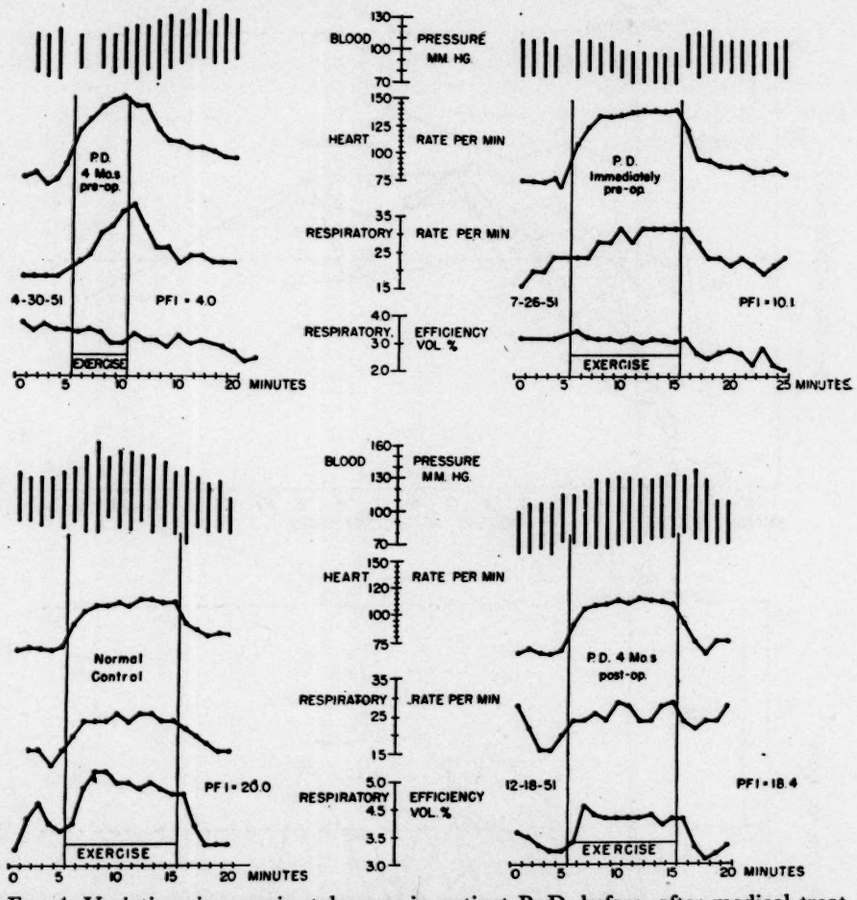

FIG. 4. Variations in exercise tolerance in patient P. D. before, after medical treatment and four months after surgical treatment, with a normal subject (in left lower quadrant) for comparison. See text for details.

for several weeks preoperatively. An increase in the respiratory efficiency is compatible with a more favorable alveolar ventilation/perfusion ratio, due to lessened hyperventilation, increased cardiac output, such as may occur with lowering of the pulmonary resistance, or both. In addition, it may reflect a decrease in oxygen content of mixed venous blood, such as occurs with stagnant anoxia from heart failure when the arteriovenous oxygen difference is increased. Under these circumstances, however, the patients are hardly ever able to continue this level of exercise for ten minutes. Only two patients, W. S. and C. McC., showed a slight decrease in

The heart rate returned to the resting level more rapidly after exercise, for the sum of the rates for the first three minutes of recovery averaged 26 less than preoperatively (range −104 to +49). Concomitantly, the average systolic blood pressure during exercise and early recovery tended to be 13 and 11 mm. Hg higher, respectively, than previously. The change in recovery heart rate suggested a decrease in the oxygen debt following surgery whereas the increase in systolic blood pressure during exercise may reflect a higher cardiac output. Neither the rebound in systolic pressure after exercise nor the apparently greater rebound

following the operation have been explained satisfactorily as yet. Possibly they reflect changes in peripheral resistance in the presence of inadequate cardiac output during exertion.

The importance of normal sinus rhythm was demonstrated in patient M. F., for none of the postoperative increment in PFI could be attributed to the operation. In this instance the PFI was not increased until the auricular fibrillation was converted to normal sinus rhythm with quinidine. (This patient has had to continue maintenance therapy with quinidine for auricular fibrillation with palpitation; dyspnea and weakness recurred whenever the drug was discontinued.) In another patient, H. C., about one-half of the postoperative increment in PFI was due to surgery; the remainder was due to the conversion to sinus rhythm with quinidine. (Fig. 2.)

The incidence of auricular fibrillation and premature ventricular systoles during exercise was somewhat lower after mitral valve surgery and effective treatment with quinidine. There was only a slight reduction of doubtful significance in the frequency of abnormal changes in the S-T segment or T waves of the left precordial lead electrocardiogram postoperatively. The magnitude of these deviations from normal tended to be lessened, however, and possibly some of the patients will show a normal response eventually.

The association of pulmonary fibrosis with mitral stenosis need not prevent functional improvement after mitral commissurotomy. For example, J. B., a forty year old woman with symptoms attributed to mitral stenosis for thirteen years, was found to have markedly increased total pulmonary arterial resistance of 1,980 dynes sec. cm.$^{-5}$ at rest during cardiac catheterization. The PC pressure was not obtained but the LA pressure at surgery was the lowest of the entire group, 11 mm. Hg. There was calcification of the stenotic mitral valve. The left lung was firm and rubbery when examined during thoracotomy. Biopsy of the tip of the lingula showed considerable alveolar fibrosis. (Fig. 5.) In the second postoperative month she had symptoms resembling influenza and the possibility of rheumatic pneumonitis was considered. Chest x-ray examination revealed miliary nodules scattered throughout the lung fields. Despite these changes her exercise tolerance improved and she has held this improvement, without any medical treatment,

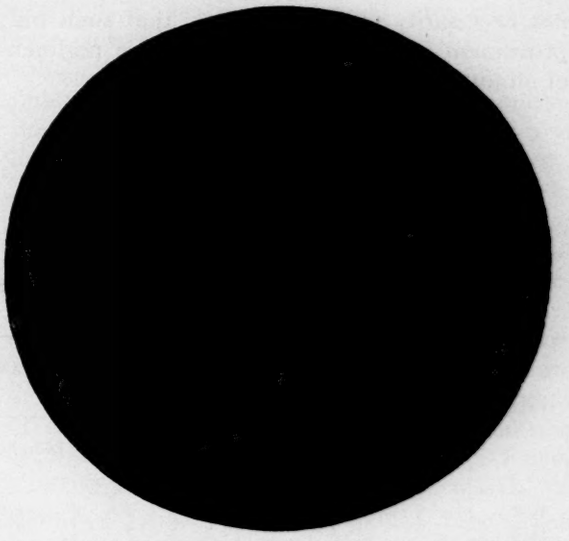

FIG. 5. Microscopic section of lung biopsy obtained from patient J. B. during mitral valve surgery; × 100. Note the alveolar fibrosis. See text for comments.

over the ensuing year. (Fig. 3A.) Although fibrotic markings in the chest x-ray have diminished in intensity, there has been no change in heart size.

Comment: Whereas the clinical appraisal indicated that fourteen of the twenty patients were improved as a result of mitral valve surgery, objective exercise tolerance tests showed varying degrees of improvement in nineteen patients. The average increase in PFI of 6.6 represented a significant change from the best preoperative performance. It is important to note, however, that this was observed postoperatively without the benefit of a preparatory period of bedrest and optimal regulation of the cardiac status, such as was instituted in each instance immediately prior to surgery. Disregarding this preoperative preparation, the average improvement from the initial preoperative test to the best postoperative test would be 10.3. Not all of this improvement could be attributed to the surgical procedure *per se*, for in some patients the preoperative medical treatment accounted for a substantial part of the apparent increased reserve. Furthermore, the amount of improvement associated with the conversion of auricular fibrillation to normal sinus rhythm was demonstrated in two patients. The other exercise data also demonstrate more nearly normal pulmonary and circulatory functions, without necessarily a restoration of ventricular repolarization to a normal electrocardiographic pattern. It does

not necessarily follow, however, that such improvement could be maintained on a regimen of almost unlimited physical activity.

HEART FAILURE AFTER MITRAL VALVE SURGERY

To date, seven of the twenty patients have exhibited deterioration of exercise tolerance after an initial increase following mitral valve surgery. In six of these patients the PFI declined by 1.1 to 12.8 from the highest score obtained in the postoperative period. (Table v.) This occurred from three to nine months after the operation. (Fig. 3B.) Four patients permitted themselves excessive and prolonged physical activity, and three of these had an unrestricted salt intake. Two of these patients did not receive sufficient digitalis for adequate maintenance therapy. One patient, F. C., has shown deterioration of her clinical status and impaired exercise tolerance on four separate occasions within the first year following surgery. (Fig. 3B.) Two other patients presented electrocardiographic evidence of digitalis intoxication. When the dosage was reduced their exercise tolerance deteriorated. Finally, one patient, G. S., could not tolerate any preparation of digitalis or squill. Two months after the operation her PFI was only one-half of its preoperative value. She continued to have a pleural effusion for several months. After nine months she exhibited significant clinical improvement and showed an increase in the PFI despite the fact that she was never digitalized.

Along with the decline in PFI when exercise tolerance diminished, the ability to endure the standardized exercise stress decreased by 2.7 to 7.6 minutes in five of the seven patients. The average respiratory efficiency during exercise declined in all instances whereas the responses in heart rate and blood pressure were variable.

Comment: These changes in functional capacity, usually occurring months after surgery, are interpreted as evidence of heart failure. The importance of subsequent heart failure has not received sufficient attention in current reports evaluating the effects of mitral valve surgery. Possibly this is due to the fact that it may not be clearly apparent because of the paucity of physical signs. The chief complaints noted by the patient are fatigue and dyspnea on exertion, as well as orthopnea and palpitation at rest. There may be no striking evidence of congestive heart failure in terms of pulmonary edema or hepatomegaly and peripheral edema. These features are not likely to be conspicuous unless there has been considerable salt retention with expansion of the extracellular fluid compartment. Lacking these manifestations, an objective test of working capacity then becomes a useful guide to the clinical management of patients who complain of these symptoms. In most instances it has been possible to demonstrate improvement in the PFI, together with at least partial relief of symptoms when the usual measures for the treatment of cardiac decompensation are employed; namely, rest, larger doses of digitalis, reduced intake of salt and, in extreme cases, mercurial diuretics. As yet it has not been possible for five of the seven patients to regain fully the former highest postoperative PFI value. None of these patients have presented either clinical or biopsy evidence of "rheumatic activity." Some patients have experienced an

TABLE V

POSTOPERATIVE DETERIORATION IN EXERCISE TOLERANCE ATTRIBUTED TO HEART FAILURE

Patient	Elapsed Time from Operation (mo.)	Symptoms	Endurance (min.)	PFI	Comparsion with Best Postoperative Test. Changes in:				Systolic B.P.		Reasons for Failure*
					Endurance	PFI	R.E. (Ex)	HR (3 min R)	Ex.	Rec.	
F. B.	5	D, F, Pa	5.1	5.8	−4.9	−11.9	−1.3	+ 35	+10	+ 6	1, 2
C. B.	3	D, LP	10.0	9.3	0	− 4.4	−2.0	− 36	+ 5	− 2	1
J. D.	6	D, F	3.5	5.6	−4.0	−10.7	−0.6	+ 51	− 1	+20	4
G. S.	4	D	2.0	2.0	−2.7	− 2.2	−0.2	− 51	− 5	− 6	5
E. B.	3	D	10.0	13.8†	0	− 1.1	−0.1	+ 16	0	+ 2	2, 3
F. C.	9	D, LP	4.5	4.5	−5.5	−12.8	−0.6	+112	−15	0	2, 3, 4
H. K.	7	D, P, LP	6.0	6.5	−7.6	− 4.0	−0.7	+ 44	−25	+18	2, 3

* (1) Inadequate maintenance dose of digitals; (2) excessive physical activity; (3) uncontrolled salt intake; (4) digitalis dosage reduced because of evidence of intoxication; (5) intolerant of any digitalis preparation, also had persistent pleural effusion postoperatively.

† Results obtained almost 1 month after hospitalization for the first episode of congestive heart failure.

influenza-like state transiently in the postoperative state. Yet it is doubtful if this can be interpreted as "rheumatic pneumonitis" for there has been no evidence of carditis or deterioration of function during such intervals.

OBSERVATIONS

The salient physiologic effects of advanced mitral stenosis are a rise in pressure in the left auricle, which is reflected in increments in pressure in the pulmonary veins, capillaries and arteries, and a decrease in the cardiac output, especially on exertion. The pulmonary arterial resistance increases as the arterioles become narrowed, presumably by vasoconstriction initially and subsequently by intimal proliferative and degenerative changes. Finally, the right heart dilates and peripheral congestive manifestations ensue. Although many of these changes are reflected in symptoms and signs of mitral stenosis, pulmonary engorgement, hypertension and right heart failure, the quantitative appraisal heretofore has rested largely on the technic of venous catheterization of the heart. Unfortunately this procedure is relatively complex. In the opinion of the authors its chief value is in obtaining a measure of the left auricular pressure indirectly through the pulmonary capillary pressure and in estimating the cardiac output. The changes in both may be evaluated with respect to transient mild exercise, usually performed with the legs while the patient is supine. This may not be entirely representative of the physiologic effects of exercise in the upright posture, due to differences in hydrostatic pressure relationships, as well as the unaccustomed form of exercise.

There are several changes in the physiologic responses to exercise which may be observed in patients with mitral stenosis: (1) The ability to increase the systolic blood pressure during exertion is often impaired. In advanced cases of mitral stenosis the pressure may actually fall below the resting level. (2) After the exercise is completed the pressure frequently shows an abnormal rebound between the first and fifth minutes of recovery. Both the magnitude and the time of onset of these changes vary in different individuals. Presumably the decline in systolic pressure during exertion represents a diminished cardiac output but it has not been feasible to demonstrate this by the direct Fick principle because of the extra hazard in poor-risk patients. (3) Respiratory efficiency during exertion is usually subnormal and may be even lower, paradoxically, than the resting value in patients with marked changes in pulmonary hemodynamics and hyperventilation. (4) There is tachycardia during effort and delayed return to the resting level in recovery. This is particularly marked during exercise in patients with auricular fibrillation who are not fully digitalized. (5) The precordial lead electrocardiogram often shows abnormal responses indicative of impaired myocardial function. Ventricular premature systoles are more likely to occur during the second minute of exercise, and rarely there are short paroxysms of ventricular tachycardia without palpitation or other symptoms. Depression of the S-T segment and either inversion of T waves, or pathologic, high voltage, upright T waves may be demonstrated during exercise. Changes in repolarization may persist in some patients for a minute or longer in the recovery phase. (6) Tachypnea usually accompanies a reduction in the respiratory efficiency during exercise. Previous studies have demonstrated a relationship between the respiratory efficiency and 100 times the reciprocal of the respiratory rate.[14] (7) Endurance is shortened when the heart decompensates. Under these circumstances the standardized exercise stress represents the maximal working capacity of the patient, and endurance is the chief factor in determining the physical fitness index. Occasionally, patients with congestive heart failure are unable to walk long enough to demonstrate either tachycardia, tachypnea or a subnormal respiratory efficiency. Rarely the respiratory efficiency is a high normal value, probably due to a very low oxygen content of mixed venous blood. (8) The physical fitness index is a useful quantitative measure of the integrated cardiorespiratory capacity for exercise of moderate intensity and permits, by means of a single test, an evaluation of the functional capacity of a wide range of patients varying from clinical ratings of IA to IVD, inclusive. Although the motor-driven treadmill is preferable because it standardizes the rate of energy expenditure, the same principles of evaluation have been applied to a simple step test.[14] Furthermore, the requirement of a continuous analysis of the expired air oxygen concentration may be substituted by counting the respiratory rate during exertion. Thus it is possible to determine, in a semi-quantitative fashion, the functional working capacity, as

well as changes in blood pressure and precordial lead electrocardiogram, in office practice.

The exercise tolerance test has been useful in evaluating the patient's disability due to mitral stenosis and changes that occur in the natural history of the disease. From the data obtained from the exercise tolerance test, working capacity depends upon many variables such as heart rate, cardiac output, blood pressure, ventilation, myocardial function, and their many interrelations. Serial tests also provide quantitative data on the improvement in functional capacity that may occur with either medical or surgical treatment. In selecting patients for mitral valve surgery it is not enough to be satisfied with the diagnosis but one must also be sure of the degree of relative disability, unless the surgery is proposed for exceptional circumstances. (These include prophylactic treatment of the mitral stenosis in the absence of disability in a patient being submitted for ablation of the left auricular appendage because of repeated arterial emboli, and the young woman in the child-bearing age who has had congestive heart failure during pregnancy and yet may be well compensated and asymptomatic between pregnancies.[15]) Furthermore, it is important to be sure that there is minimal cardiac reserve for surgery. Medical treatment, including prolonged bedrest, has increased the exercise tolerance of some patients to the point where they become reasonable risks for surgery. On the basis of this program for demonstrating both disability and adequate reserve there has been no operative death due to poor selection of patients in this small series. Such a program of evaluation and selection of patients for mitral valve surgery may become the final step in virtually eliminating the operative mortality.

The experience to date has been too limited to offer any definite conclusions about the relative merits of anterolateral commissurotomy, posterior valvulotomy or dilatation of the orifice. It seems, however, that more importance should be attached to the magnitude of the increased orifice, as well as its position and function during ventricular systole, than on the particular technic of accomplishing it. It has been gratifying to observe that conspicuous improvement may follow only modest dilatation of the orifice. This tends to confirm the opinion that functional disability occurs within the relatively narrow range of 0.5 to 1.5 cm^2 cross sectional area.

SUMMARY AND CONCLUSIONS

1. The exercise tolerance of twenty patients with mitral stenosis has been estimated serially to evaluate the effects of medical and surgical treatment. The exercise stress has been standardized by having the patients walk slowly on a motor-driven treadmill ergometer. The exercise tolerance was quantitated in terms of the physical fitness index.

2. Repeated exercise tests showed a satisfactory degree of reproducibility when there was no apparent change in the clinical status of the patients.

3. In most instances there was demonstrable evidence of disability or impaired exercise tolerance when the patients were evaluated initially.

4. Preoperative preparation, with particular reference to bedrest as well as optimal regulation of digitalis, dietary intake of sodium and diuretics, was found to be effective in eighteen of twenty patients. The degree of improvement varied over a wide range.

5. Both the degree and the rate of improvement in exercise tolerance were determined after mitral valve surgery. The effects of surgery could be differentiated from those due to preoperative preparation and postoperative treatment. Although 70 per cent of the patients were improved clinically, the improvement was delayed in about one-half. The majority eventually demonstrated significant increments in exercise tolerance.

6. The importance of converting auricular fibrillation to normal sinus rhythm with quinidine therapy was demonstrated with respect to increased exercise tolerance postoperatively.

7. Continued postoperative follow-up tests revealed deterioration of functional capacity in seven of twenty of the patients studied from three to nine months after operation. The common factor apparent in all in this group was attributed to heart failure resulting from one or more variables.

8. Exercise tolerance tests are an important adjunct to the clinical evaluation of patients with mitral stenosis in determining disability, minimal reserve for surgery, separating the effects of medical and surgical treatment and revealing postoperative complications, such as heart failure, that may not be appreciated by clinical examination.

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Certain Abnormal Circulatory Dynamics of Mitral Stenosis Associated with a Major Degree of Regurgitation*

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THE recent advances in mitral valve surgery for the treatment of patients with rheumatic heart disease[1–3] have stimulated studies of the physiologic changes resulting from stenosed or insufficient valvular orifices. For this reason a study was undertaken of patients with mitral valvular disease in an effort to determine whether any particular dynamic abnormalities might be recorded by means of the ballistocardiogram and the electrokymogram. The purpose of this paper is to report the abnormalities seen in the ballistocardiographic and electrokymographic recordings of these patients especially in reference to mitral insufficiency and to discuss their mechanisms of production.

MATERIAL AND METHODS

Selection of Patients. The individuals used in this study had chronic rheumatic valvular disease, with signs and symptoms of progressive disability. All of the patients were admitted to the Hospital and Clinic of the University of Pennsylvania for evaluation for mitral valve surgery. The patients selected for study showed evidence of mitral stenosis with or without mitral insufficiency. The presence of mitral stenosis was based on the finding of a characteristic mitral diastolic murmur and enlargement of the left auricle. The criteria for evaluating the presence of a major degree of mitral insufficiency were: (1) a loud systolic murmur heard at the mitral area, occasionally accompanied by a palpable thrill; (2) a markedly dilated left atrium sometimes with systolic expansions demonstrable by fluoroscopy; (3) an enlarged left ventricle in the absence of aortic regurgitation and/or stenosis; (4) an angiocardiographic study showing rapid opacification of a large left ventricle, following the appearance of diodrast in the left atrium[4] and (5) a regurgitant jet, felt by the surgeon during operation, coming up through the mitral valves into the left atrium.

All of the five clinical signs were demonstrable in six of this series of ten patients with mitral stenosis associated with a major degree of regurgitation. Among the remaining four patients two of them had four and the other two patients had three of the five clinical criteria for the diagnosis of a dynamically significant degree of mitral regurgitation.

Method of Study. The special studies generally began by recording simultaneously the patient's ballistocardiogram, phonocardiogram and electrocardiogram. In order to ensure cooperation and relaxation on the part of the patient the procedure was explained to him while he rested for twenty minutes in the recumbent position prior to the test. Patients were instructed to stop respiratory movements momentarily, without straining, when a tracing was being taken. The patient then sat up for the electrokymographic study. In this position kymographic recordings were made of the border movements of the inflow tract of the left ventricle and of the left atrium, whenever possible. Later an intra-aortic pressure curve was recorded through a small plastic catheter advanced from the femoral artery to the ascending aorta under fluoroscopic guidance. Aortic pressure curves were usually combined with recordings of heart sounds and electrocardiograms or ballistocardiograms. The study was subsequently

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FIG. 1. Ballistocardiogram of patient E. N., who was found to have a marked degree of mitral stenosis and a relatively small degree of regurgitation at operation, taken simultaneously with phonocardiogram and electrocardiogram. A small early systolic headward wave, indicated by arrow, is seen in front of the J wave in the ballistocardiogram.

completed with right heart catheterization, at which time pressure curves of pulmonary "capillary," pulmonary artery, right ventricle and right atrium were recorded simultaneously with the phonocardiogram and the electrocardiogram.

Recording Methods and Equipments. Right heart catheterization was performed according to the technic of Cournand and Ranges.[5] Pulmonary "capillary" pressure was recorded by the method described by Lagerlöf and Werkö[6] and Hellems, Haynes and Dexter.[7] The ascending aorta was catheterized by the small plastic catheter technic developed by Peterson, Schnabel, Fitzpatrick and their associates.[8–9] Pressures were recorded through large Cournand or small plastic catheters attached to a Lilly capacitance manometer. The time lag of this system is 0.002 second or less. Ballistocardiograms were taken with an electromagnetic type of Dock-Taubman ballistocardiograph.[10] The instrument had previously been standardized against the Starr-type table ballistocardiograph. The ballistic waves recorded simultaneously with these two types of machines were found to check accurately in form and timing.[11] The electrokymograph* used in this study was the type developed by Henny, Boone and Chamberlain.[12–13] The time lag of this particular instrument has been calibrated at 0.015 seconds within a frequency range of 1–35 cycles per second. A Sanborn tribeam machine which includes a phonocardiographic channel was used for all the recordings in this study.

*Manufactured by the Cambridge Instrument Company.

RESULTS

Ballistocardiographic Pattern of Patients with Mitral Stenosis Associated with a Significant Degree of Mitral Regurgitation. The ballistocardiogram of each of the ten patients with mitral stenosis associated with clinical signs of a significant degree of mitral regurgitation showed a characteristic abnormal pattern. It consisted of a roughly M-shaped systolic complex, created by the addition of an early systolic, headward ballistic wave to the usual later systolic upward deflection, commonly designated as the J wave. This headward early systolic wave was observed to begin from 0.08 to 0.14 second after the Q wave of the electrocardiogram, and 0.02 to 0.08 second after the onset of the main vibrations of the first heart sound, reaching its peak in 0.06 to 0.07 second. In these cases the onset of the J wave which came after the early systolic headward deflection was usually delayed. The amplitude of this early systolic headward wave relative to that of the J wave varied a great deal from one patient to another. The early systolic headward wave was either not present or of small amplitude in those patients who showed clinical signs of marked degree of mitral stenosis with little evidence of regurgitation. Figure 1 shows an example of the ballistocardiogram of such a patient. It was obtained from patient E. N., with rheumatic heart disease, clinical evidence of a marked degree of mitral stenosis and auricular fibrillation. The right ventricle and left atrium were found to be enlarged by fluoroscopic and electrocardiographic studies. Angiocardiogram showed a

FIG. 2. Ballistocardiogram of patient R. B., with a fairly marked degree of mitral insufficiency proven at operation, shows a large and sharp early systolic headward wave, indicated by arrow in each ballistic complex.

concentration of diodrast in the left atrium, with moderately rapid opacification of the left ventricle. At operation a satisfactory opening of the commissures was achieved by the finger fracture technic but the surgeon was uncertain as to the size or the character of the orifice. Phonocardiogram showed a loud diastolic murmur lasting practically the entire length of the diastole and a short vibratory early systolic murmur coming after a much accentuated first heart sound. The ballistocardiogram shows a very small upward deflection in front of the J wave in the early part of the ventricular systole.

This early systolic headward ballistic wave approached and might even exceed the size of its respective J waves in patients who show signs of a major degree of mitral regurgitation. An example of such a double-peaked ballistocardiographic pattern is shown in Figure 2. This record was taken on patient R. B., with rheumatic heart disease, mitral stenosis and insufficiency, aortic insufficiency and auricular fibrillation. He suffered from repeated bouts of pulmonary edema and had a moderate degree of dyspnea at all times. All therapeutic measures failed to control his heart failure. Mitral valve surgery was attempted at another hospital. At operation the mitral valve leaflets were found to be rigid and insufficient. A large regurgitant jet was felt by the surgeon in the left atrium. Because of the wide mitral opening a mitral commissurotomy could not be performed on this patient. The ballistocardiogram shows a large and sharp upward deflection in early ventricular systole just before the tall spiking J wave.

The ballistocardiograms of two of our patients with predominating mitral insufficiency showed in addition to the double-peaked systolic ballistic complex, a deep V-shaped footward wave 0.06–0.08 second after the end of the second heart sound.

Differentiation of the Early Systolic Headward Wave from the H Wave of Auricular Activity in the Ballistocardiogram. The early systolic headward wave seen in individuals with a significant degree of mitral regurgitation can usually be distinguished from the H wave of auricular origin by noting its position in the cardiac cycle. This early systolic headward wave starts during ventricular systole, 0.08 to 0.14 second after the Q wave in the electrocardiogram, while the auricular H wave begins before the Q wave and reaches its peak near the top of the QRS complex of the electrocardiogram.

In order to demonstrate that the early systolic headward wave is different from the H wave of atrial origin, patients were selected with mitral valve disease in whom sustained auricular activity was either absent or widely separated from the ventricular contraction. These conditions were found in patients with: (1) auricular fibrillation and (2) prolonged auriculoventricular conduction time.

Figure 3 shows a ballistocardiogram taken on patient M. S., who showed physical signs of mitral stenosis with a moderate degree of regurgitation and auricular fibrillation. At operation the mitral valves were found to be rigid and were held partially open by dense fibrous tissue and calcific deposits. A definite regurgitant jet was felt in the left atrium. In the ballistocardiogram a fairly prominent upward deflection can be identified in each of the ballistic complexes during the early part of the ventricular systole throughout the tracing. The electrocardiogram shows auricular fibrillation.

Figure 4 is a tracing from patient E. W., who showed signs of mitral stenosis, complicated

FIG. 3. Ballistocardiogram of patient M. S., with mitral stenosis associated with a moderate degree of mitral regurgitation and auricular fibrillation. Arrow indicates the prominent early systolic headward wave in each ballistic complex.

FIG. 4. Ballistocardiogram of patient E. W., with mitral stenosis associated with a moderate degree of mitral regurgitation and second degree A-V heart block. A prominent early systolic headward wave can be seen in each of the four ballistic complexes, unrelated to the P waves in the electrocardiogram.

with a moderate degree of regurgitation. He also had a second degree A-V heart block resulting from digitalis administration. The patient's condition was satisfactory and he was able to continue on with his work as a roll-taker in an arsenal. Following an attack of acute upper respiratory tract infection he developed pneumonia of the left upper and right lower lobes, and auricular flutter with a ventricular of 150 per minute. He did not respond to various therapeutic measures and died of acute pulmonary edema four days after his admission to the hospital. At postmortem examination the mitral valves were found to be quite stenotic. The valvular edges and chorda tendinae were found to be thickened, fibrotic and shortened, leaving a defect at the center. A study of his ballistocardiogram shows a sharp upward deflection in front of the J wave in each of the ballistic complexes. The early systolic headward waves seen in the beats with markedly prolonged P-R intervals (Cycles 1 and 2) are just as prominent, if not more so, than in those beats where the P-R intervals are shorter. These examples clearly indicate that the auricular contraction is not responsible for the production of this early systolic headward ballistic movement in these patients.

Differentiation of Ballistic Complex Seen in Patients with a Significant Degree of Mitral Regurgitation from a Bifid Ballistic Complex Due to Ventricular Asynchronism. Electrokymograms of the aorta and pulmonary artery were taken in succession on each of the patients studied. Each kymogram was timed with phonocardiogram and lead II electrocardiogram according to the method described by us in a previous study.[11] In each individual the onset of the pulmonic and of the aortic pulsations were found to differ in time from 0.01 to 0.03 second, which was well within the range of technical error of this study. It is of significance to note that the patients in this series who showed M-shaped ballistic complexes, which we attribute to the presence of an additional early systolic headward deflection as a result of mitral insufficiency, did not have a greater time interval between the onset of the aortic and pulmonic ejections than those whose ballistocardiograms were more normal in appearance.

Differentiation of the Dynamics Associated with the Early Systolic Wave Seen in Patients with Mitral Regurgitation from Those Associated with the J Wave. In attempting to prove that the early systolic headward wave is not in any way related to the ballistics that produce the J wave, pressure curves from the ascending aorta were recorded simultaneously with the ballistocardiogram.

FIG. 5. A, ballistocardiogram of patient A. R., with moderately large degree of mitral regurgitation, taken simultaneously with phonocardiogram and pressure curves of the ascending aorta. The large early systolic headward ballistic wave indicated by arrow starts before the onset of the aortic pulse. The aortic pulse wave starts later than normal. B, ballistocardiogram of patient C. S., with mitral stenosis and very little regurgitation, taken simultaneously with pressure curves of the ascending aorta, shows no early systolic headward wave. Onset of the aortic pressure curve coincides with the I wave in the ballistocardiogram and occurs earlier in the cardiac cycle than in Figure 5A.

An example of such a study is shown in Figure 5A. This tracing was made on patient A. R. who has mitral stenosis with evidence of a moderately large degree of mitral regurgitation, as shown by a loud blowing systolic murmur at the mitral area, a very large left atrium with systolic pulsations, auricular fibrillations, electrocardiographic and roentgenologic evidences of left ventricular enlargement, and angiocardiographic demonstration of marked enlargement of the left cardiac chambers. At operation the mitral orifice was found to be moderately insufficient and a regurgitant jet was felt in the left atrium. The ballistocardiogram shows a large early systolic headward wave in each ballistic complex. A comparison between the timing of the intra-aortic pressure curve and the ballistocardiogram shows that the onset of the aortic pulse wave is delayed, occurring near the peak of the early systolic headward wave. Since this headward wave has already started to swing upward before the aortic pulse begins, it would appear that the early systolic headward wave is not produced by the forces of systolic ejection of blood into the aorta. Furthermore, it can be presumed that because of the regurgitation of blood into the atrium, aortic ejection is both delayed and weakened, resulting in a shift of the onset of the J–K waves in the ballistocardiogram to a later part of the cardiac cycle.

Figure 5B was taken from a similar study made on patient C. S., who has mitral stenosis with little clinical evidence of mitral regurgitation. The ballistocardiogram shows no early systolic headward wave. A correlation between the ballistocardiogram with the intra-aortic pressure curve indicates: (1) the onset of the rise in the pressure curve coincides with a small downward deflection (I wave), and is definitely before the J wave; (2) both the aortic pressure curve and the main ballistic complex appear much earlier in ventricular systole than in Figure 5A.

Left Ventricular Electrokymographic Pattern of Patients with Mitral Stenosis Associated with a Major Degree of Mitral Regurgitation. Patients who showed clinical signs of mitral stenosis with a major degree of mitral regurgitation had very abnormal left ventricular border movements which could be recorded by the electrokymographic method. Figure 6A shows the electrokymographic pattern in patient A. R., whose ballistocardiogram was presented in Figure 5A. The kymographic pattern is characterized by a sharp upward swing of the curve, representing a rapid lateral movement of the left ventricular wall, beginning with the second heart sound.

FIG. 6. A, left ventricular electrokymogram of patient A. R., (whose ballistocardiogram is shown in Fig. 5A) shows a sharp upward swing of the kymographic curve, reaching its peak in early diastole. Phonocardiogram and electrocardiogram were taken simultaneously for timing purposes. B, left ventricular electrokymogram of patient L. M., with marked mitral stenosis and little regurgitation, shows a slowly rising kymographic curve reaching its peak just before the onset of the subsequent ventricular systole.

The curve continues rapidly upward to its peak in early diastole and is maintained at the high level throughout the remainder of the diastole. With the onset of ventricular systole and medial movement of the ventricular wall the kymographic curve drops rapidly to the base line. In two instances in which a marked degree of regurgitation was present the protodiastolic rising limb of the left ventricular kymographic curve was sharper and rose more abruptly than the descending limb of the curve representing ventricular systole.

Figure 6B shows a similar electrokymographic study made on patient L. M., who had classical signs of mitral stenosis with little evidence of insufficiency which was subsequently confirmed at operation. The electrokymographic pattern of the left ventricular border movements is quite different from that which has been described above. The left ventricular "filling" curve is more normal in appearance and starts to swing upward in a gradual slope several hundredths of a second after the end of the second heart sound. Its peak is reached at the time of the first heart sound in the subsequent cardiac cycle.

Left Atrial Electrokymographic Pattern of Patients with Mitral Stenosis Associated with a Major Degree of Mitral Regurgitation. Electrokymographic tracings of the border movements of the enlarged left atrium could be obtained in only three of the ten patients who had clinical signs suggestive of the presence of a dynamically significant degree of mitral regurgitation. The kymographic records tend to confirm the impression of an expansile pulsation of the atrium which one sees in the fluoroscope with each ventricular contraction.

Figure 7A shows a kymogram of the left atrium of patient M. S. who has chronic rheumatic valvular disease, severe congestive heart failure and the following clinical signs suggestive of a marked degree of mitral regurgitation: (1) a loud systolic murmur heard throughout ventricular systole at the mitral area; (2) an enormous left atrium which pulsated during ventricular systole and (3) an enlarged left ventricle. The kymographic curve indicates a rapid outward movement of the left atrial border almost immediately after the ventricle has started to contract. The outward movement rapidly reaches its maximum, and the atrium remains distended throughout the duration of the ventricular systole. The curve then dips sharply to the base line by a quick mesial movement of the atrial border following the relaxa-

FIG. 7. A, electrokymogram of the border movement of the left atrium from patient M. S., who had mitral stenosis associated with a marked degree of regurgitation, shows a sharp upward movement of the curve following ventricular contraction and remains elevated during the entire period of ventricular systole. The kymogram is taken simultaneously with electrocardiogram and phonocardiogram. B, patient M. S., right ventricular pressure curve taken simultaneously with phonocardiogram and electrocardiogram. Note the similarity between the contour of the ventricular pressure curve and the left atrial EKY.

tion of the left ventricle. It is interesting to note that the contour of the right ventricular pressure curve of this patient shown in Figure 7B is practically identical with the left atrial kymographic pattern presented in Figure 7A. Since there is no appreciable asynchronism between the two ventricles, it may be assumed that the general contour of the left ventricular pressure curve, except for higher amplitudes, is in most ways similar to that which is recorded in the right ventricle.

Pulmonary "Capillary" Pressure. The pulmonary "capillary" pressure curves obtained in this series of patients with mitral stenosis complicated with a major degree of mitral regurgitation have generally been unsatisfactory in predicting the degree of mitral insufficiency. In most cases the undamped record usually contains numerous artefacts, while a less sensitive recording shows waves of low amplitudes. On two occasions in which the patients came to surgery we found considerable discrepancies between the pulmonary "capillary" pressures obtained by catheterization and the left atrial pressures measured by direct puncture of the atria during operation.

COMMENTS

In experimental mitral insufficiency Wiggers and Feil[14] and Lanari and Molins[15] demonstrated a rapid rise in the left atrial pressure with each ventricular contraction. The latter observers also found that if the regurgitation were severe, left atrial pressure rose to sudden high levels and pulmonary edema developed. In human mitral insufficiency a similar sharp rise in the left atrial pressure with ventricular contraction, together with a palpable regurgitant jet, is often demonstrable during mitral valve surgery.[16,17] These experimental and clinical observations suggest that the forces exerted by the systolic back-flow of blood through the incompetent mitral valves might produce ballistic effects analogous to those forces exerted by the flow of blood into the aorta and the pulmonary artery. Ballistocardiographic studies made on patients with clinical signs of a major degree of mitral regurgitation consistently showed a large headward ballistic wave in front of the J wave with each ventricular systole.

After identification of this wave various studies were designed to differentiate this headward ballistic wave from the normal H and J waves in the ballistocardiogram and from the bifid systolic ballistic complexes of asynchronous ventricular ejections. The data obtained from these studies appear to confirm the clinical impression that the early systolic ballistic wave observed in patients with rheumatic valvular

disease is produced by the movement of blood back through the incompetent mitral valves.

Similar appearing ballistocardiographic patterns have been observed in patients with severe myocardial damage following coronary artery disease. The exact mechanism of production of a headward ballistic wave in front of the J wave in these patients is not clear. On the basis of our observations, however, the ballistocardiographic pattern seen in patients with arteriosclerotic heart disease could be either a bifid J wave resulting from ventricular asynchronism, or might be due to the presence of a large auricular H wave in front of the J wave. The possibility that these factors played a part in the production of the early systolic headward wave in our patients with a major degree of mitral regurgitation have been carefully excluded.

In a previous study we demonstrated two upward ballistic deflections during ventricular systole in patients who had marked degrees of asynchronisms between the ventricles.[11] It was suggested that the earlier of the two deflections might sometimes be labeled as an "H" wave. The present study shows that a more common cause for a similar headward ballistic deflection occurring before the J wave, at least in patients with mitral heart disease, is the back-flow of blood through the incompetent mitral valves. This early systolic headward wave could have been misinterpreted as an "H" wave in patients with auricular fibrillation, and perhaps as a notched J wave in patients with an H wave of auricular origin.

In addition to showing a headward wave in early systole, ballistocardiograms of patients with a major degree of mitral regurgitation also show a shift of the J-K waves to a later part of the cardiac cycle. The cause of the delay of J and K waves could be explained as follows: (1) during the early period of ventricular systole blood regurgitates into the left atrium; (2) this actually reduces ventricular volume; (3) as a result, the rise in ventricular pressure is slow so that the aortic valves open somewhat later in the cardiac cycle than usual. Preliminary studies suggest that similar mechanisms might be involved in the production of a "late J-K stroke"[20] in patients with diseased myocardium and marked dilatation of the ventricles associated with an apical systolic murmur suggestive of mitral insufficiency but no evidence of valvular lesion.

In two of these patients with mitral stenosis complicated with a major degree of mitral regurgitation, besides the double-peaked headward systolic ballistic complex, a large negative V-shaped wave was recorded. This early diastolic ballistic wave is probably related to rapid ventricular filling.

A characteristic systolic elevation in the left atrial electrokymographic tracing in cases of mitral valve disease was reported by Luisada and Fleischner[21] and McKinnon and Friedman.[22] This kymographic finding is thought to represent regurgitation of blood through the insufficient mitral valves. We have been able to obtain similar tracings in a few of our patients but in most cases it was technically difficult or impossible to make satisfactory kymographic studies of the atrial movements.

Since left ventricular filling, in the absence of aortic insufficiency, is entirely dependent upon the rate of flow of blood through the mitral orifice, a study of the pattern of left ventricular filling curve can be expected to provide useful information as to the relative degree of insufficiency of the mitral valves. We have found that in patients with mitral valve disease a slowly rising electrokymographic curve of the in-flow tract of the left ventricle in diastole is useful in ruling out a dynamically significant degree of mitral regurgitation. When cardiac failure is present in a patient with mitral stenosis, a slowly rising left ventricular electrokymographic curve is a good indication of the presence of a "tight" valve; for this type of kymographic pattern is markedly different from the rapidly rising curve in early diastole seen in patients with cardiac failure due to other causes.

In selecting patients for mitral valve surgery Harken and his associates[3,18,19] pointed out that in a number of patients with mitral insufficiency the valvular defect may be partially or completely closed during ventricular contraction. However, in cases in which a rigid mitral orifice is directed into the out-flow tract of the left ventricle, regurgitation may be extensive although the defect may not be large. These observations indicate the need of methods for detecting movements of blood through the incompetent mitral valves, as well as those for roughly estimating the size of the valvular defect. Hence the use of electrokymographic and ballistocardiographic procedures would appear to be justified.

The electrokymographic and ballistocardio-

graphic studies have been found to be complementary to each other, and to correlate well with the clinical signs of a dynamically significant degree of mitral regurgitation. These procedures may prove to be useful adjuncts for the study of those patients with mitral stenosis in whom a major degree of mitral regurgitation is suspected.

SUMMARY

1. Electrokymographic and ballistocardiographic technics were employed in the study of the circulatory dynamics of patients with mitral stenosis with and without a major degree of mitral regurgitation.

2. A large early systolic headward ballistic wave has been identified in the ballistocardiogram of patients who have a dynamically significant degree of mitral regurgitation. In two of these patients a deep V-shaped ballistic wave was also observed in early diastole.

3. Clinical observations and various physiologic studies indicate that the forces exerted by the back-flow of blood through the incompetent mitral valves are probably responsible for the production of the headward early systolic wave in the ballistocardiogram.

4. This headward ballistic wave produced by the regurgitant stream through the incompetent mitral valves could have been misinterpreted as an H wave in patients with auricular fibrillation, and perhaps as a notching of the J wave when an atrial H wave is already present.

5. Electrokymograms of the in-flow tract of the left ventricle of patients with mitral stenosis associated with a major degree of mitral regurgitation shows a rapid lateral movement of the left ventricular wall reaching its peak in early diastole.

6. A similar electrokymographic study made on patients with a "tight" mitral stenosis, with little or no mitral regurgitation, shows a slow lateral movement of the left ventricular wall, reaching its peak just before the onset of the subsequent ventricular systole.

7. Ballistocardiographic and electrokymographic studies may prove to be useful in the study of patients with mitral stenosis in whom a major degree of mitral regurgitation is suspected.

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Ventilatory Studies in Mitral Stenosis*

A Comparison with Findings in Primary Pulmonary Disease

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As a rule, the initial symptoms in patients with mitral stenosis of rheumatic origin are related to respiration. Dyspnea provoked by effort, excitement or infection is the commonest complaint and may be accompanied by coughing, wheezing, hemoptysis or fatigue of the respiratory musculature. Generally, these symptoms are slowly progressive although they may remain stationary for many years. Only late in the disease, in the absence of complicating factors such as active rheumatic carditis, do the patients manifest widespread vascular congestion and signs of right ventricular failure.

The circulatory dynamics in mitral stenosis have been studied repeatedly in an effort to relate these pulmonary symptoms to local changes of blood pressure and flow. Even more frequent and venerable have been the descriptions of altered respiratory mechanics in cardiac disease, however, with only occasional particular reference to mitral stenosis.

Von Basch,[1] in 1896, demonstrated with an experimental model that pulmonary rigidity attends local vascular congestion and results in a disproportionately large residual volume; later this observation of volumetric increase was confirmed clinically. The early determinations of lung volume in cardiac disease were made on patients with rheumatic valvular lesions.[2–5] Subsequently, patients with either mitral stenosis or non-rheumatic left ventricular failure were studied without a distinction being made between the two groups.[6,7] That a significant difference does exist between them will be shown in a future report.[8]

In the general field of cardiac disease the changes in lung compartments, respiratory rate, tidal volume,[6,9–15] ventilatory equivalent,[5,16–18] intrapleural pressure,[9,19–21] and maximal breathing capacity[16] have been ascribed to pulmonary rigidity affecting distensibility and so-called elastic recoil of the lung.[2,4,6,9,19,22–27] Reduced alveolar ventilation has also been demonstrated.[11,13,14] However, there has been no evidence of a gross defect in the mixing and distribution of gas, as measured by the residual alveolar nitrogen following the breathing of high oxygen mixtures.[28]

It has been frequently asserted that impairment of pulmonary distensibility contributes to cardiac dyspnea by causing excessive activity of the Hering-Breuer reflex[9,10,25,26] resulting in hyperventilation with shallow, inefficient breathing,[13,14,18] and by necessitating a greater respiratory muscular effort for a constant volumetric exchange.[10,26,29] A critical lowering of the vital capacity has also been thought to be a reflex cause of dyspnea;[22] great value has been placed on this measurement as an accurate index of disability.[30,31]

In the present study the pattern of defective ventilation in mitral stenosis, together with factors important in its genesis, will be described. Its role in the causation of symptoms and its usefulness in the clinical appraisal of patients will be discussed. Finally, the functional results in mitral stenosis will be compared with those encountered in obstructive and restrictive pulmonary diseases to seek any differences which might be of diagnostic value.

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MATERIAL AND METHODS

Sixty-two patients with rheumatic heart disease were studied in whom mitral stenosis was the predominant valvular lesion. Patients were excluded if they had prominent backgrounds of bronchopulmonary infection. The New York Heart Association classification of functional capacity[32] was used: Class I comprised patients without limitation of physical activity; Class II, those with slight to moderate limitation; Class III, those with moderate to great limitation and, Class IV, those unable to perform any activity without discomfort.

During the present study the terms "functional capacity" and "disability" were given more prominence than the term "dyspnea." Although the patients were closely questioned about symptoms, they could not always distinguish among weakness, fatigue or dyspnea. Several patients had become used to applying the term "shortness of breath" to all three. To eliminate the difficulty of evaluating separately these symptoms they were united into the single term "disability."

Clinical, fluoroscopic, roentgenographic and electrocardiographic observations were made and the relevant findings are listed in Table 1. The criterion of Ungerleider and Gubner,[33] which relates the greatest transverse diameter of the heart to height and weight, was used to estimate roentgenographic enlargement.

The studies were made without special preparation of the patient but were interrupted by suitable rest periods. Several tests were employed to measure the capacity for dynamic exchange of air. The maximal breathing capacity was measured while patients breathed through a high velocity respiratory valve. The expired gas was collected in a Douglas bag for fifteen seconds. The thirty-second collection period, used by us in previous studies of pulmonary disease, was impracticable because of the frequent occurrence of dyspnea and fatigue during the second half of the test. The volume of gas was converted to liters per minute at BTPS (body temperature, ambient barometric pressure and saturated with water vapor). The best of three efforts was compared with predicted normal values based on age, sex and body surface area.[34] The upright vital capacity was measured with a spirometer with an attached timing device which permitted measurements of the fractions of the total volume moved during the first three, two or one second intervals.[35,36] Normal individuals are able to exhale an average of 97 per cent of their total vital capacity in the first three seconds, 94 per cent in the first two seconds and 83 per cent in the first second.[36] Predicted normal values for vital capacities were based upon the patient's age, sex and height.[34] The vital capacity was also measured with the patient in the supine position.

The air velocity index was calculated for each patient from the formula:

$$\frac{\%\text{ of predicted maximal breathing capacity}^{37}}{\%\text{ of predicted vital capacity}}$$

When the ventilatory defect is primarily due to increased air flow resistance or loss of pulmonary elastic tissue the index is significantly less than 1.0. The index becomes greater than 1.0 when loss of aerated pulmonary tissue predominates.

The total lung capacity and its subdivisions were determined with the patients in the supine position and expressed at BTPS. The nomenclature proposed by a committee of respiratory physiologists was used.[38] The vital capacity was obtained by summing the largest of several inspiratory capacity and expiratory reserve volumes, recorded by closed spirometry. At least one recording of the expiratory reserve was made following a quiet inspiration. Functional residual capacities were measured by an open-circuit oxygen-dilution method[39] which was somewhat modified.[40] Duplicate determinations were carried out and measurements were repeated whenever results varied by more than 100 ml. or 10 per cent. Intrapulmonary mixing indices were obtained simultaneously to estimate the adequacy of gaseous distribution within the lung.[34] The mixing index expresses the percentage of nitrogen remaining in the respiratory passages after seven minutes of pure oxygen breathing. In our experience this value has not exceeded 1.5 per cent among normal subjects.

It is important to point out that the predicted normal values we used were based upon residual volume expressed at STPD (standard temperature and pressure, dry). The conversion of this volume to BTPS in our patients resulted in a mean increase of this value of approximately 10 per cent.

The resting respiratory rate, minute ventilation and oxygen consumption were determined

by closed spirometry, while the patients breathed high oxygen mixtures. Minute ventilation was converted to BTPS. Oxygen consumption was expressed at STPD in the tables and at BTPS for calculation of the ventilatory equivalent by the formula:

$$\frac{\text{Minute ventilation in liters}}{\text{100 ml. oxygen uptake}}$$

The breathing reserve at rest was calculated from the formula:[34]

$$\frac{\text{Maximal breathing capacity—Resting minute ventilation}}{\text{Maximal breathing capacity}} \times 100.$$

Exercise ventilation was measured during a leisurely walk at the rate of 180 feet per minute for four minutes on a level course. Expired air was collected with a high velocity valve and Douglas bag during the last three minutes and expressed in liters per minute at BTPS. The walking index:

$$\frac{\text{Walking ventilation}}{\text{Maximal breathing capacity}} \times 100$$ represents,

in effect, the reciprocal of the breathing reserve during exercise.[41]

RESULTS

The data have been grouped according to the patients' functional disability. The following analyses were applied to the data: the arithmetic mean, the standard deviation of the mean (S.D.), the variance ratio (F) comparing variance within groups to that among groups,[42] and the coefficient of correlation (r) relating the quantitative measurement, cardiac enlargement, to ventilatory functions. The significance of the variance and correlation ratios have been expressed at the 1 and 5 per cent levels.

Class I. Among asymptomatic patients (Table I) the mean values for fractions of the vital capacity expelled per unit of time (Table II, Fig. 1), total vital capacity and the maximal breathing capacity were normal. (Table III, Fig. 2.) In recumbency the vital capacity averaged 99 per cent of predicted and in the upright position, 93 per cent. However, the two tests were not strictly comparable. In the upright position the largest single effort was chosen, whereas in recumbency the best of several inspiratory capacity and expiratory reserve volumes, obtained from the spirogram, were added together. The expiratory reserve following a quiet breath frequently was larger than that following maximal inspiration. This difference was more striking as disability increased.

Apprehension and attention to breathing probably contributed to the increased respiratory rates, minute ventilation and ventilatory equivalents in several of the younger patients in this group (Table II); hyperventilation on this basis has also been encountered among untrained normal volunteers. These factors were less prominent during exercise, thereby adding value to the walking index in estimating the ventilatory reserve. The walking index, which was normal among all the patients, averaged 14 per cent. (Table III.)

The mean values for the residual volume, total lung capacity and residual volume/total lung capacity ratio were normal. (Table III, Fig. 3.) Although individual components of the total lung capacity were occasionally increased or decreased, these variations remained within two standard deviations of the predicted value.

The index of intrapulmonary mixing was below the upper normal limit in all but two patients, neither of whom showed obvious clinical cause for the elevation. (Table III.)

Class II. With the appearance of slight to moderate disability the clinical findings, in addition to mitral stenosis, became more numerous. (Table I.) Eleven patients had abnormal electrocardiograms, eight of whom showed auricular fibrillation. The mean transverse cardiac diameter was 19 per cent greater than predicted, but only 10 per cent greater among the nine patients with normal sinus rhythm.

The timed vital capacities (Table II, Fig. 1), upright vital and maximal breathing capacities (Table III, Fig. 2) were slightly lower than in Class I. The mean values, however, remained within the normal range despite occasional significant reductions in individual patients.

The resting minute ventilation, respiratory rate, tidal volume, oxygen consumption and ventilatory equivalent were nearly the same as in Class I. (Table II.) The walking index of 18 per cent was only slightly greater than in Class I and still within normal range. The breathing reserve at rest fell to 91 per cent.

There were minimal and equal decreases in the inspiratory capacity and expiratory reserve volumes. (Table II.) Despite these changes the total lung capacity enlarged slightly due to an

increase in the residual volume. (Table III, Fig. 3.) The pulmonary resting or mid-position (functional residual capacity) was elevated. The residual volume/total lung capacity ratio was 29 per cent. Without exception, gaseous distribution, measured by the mixing index, remained unimpaired.

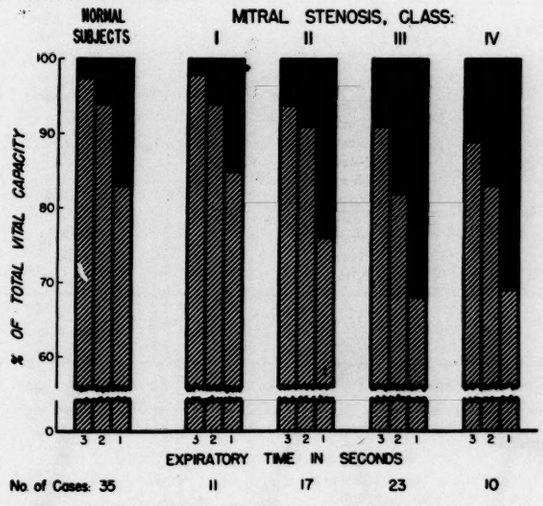

FIG. 1. Fractions of the total vital capacity exhaled during the first three seconds, first two seconds and first second of the maximal expiratory effort. Values of normal subjects and of patients with increasing degrees of disability due to mitral stenosis are shown.

Class III. Disability was moderate to severe and congestive circulatory failure, characterized by rales, rhonchi, wheezing, hepatomegaly and dependent edema, was frequently in evidence. (Table I.) There were twelve patients with auricular fibrillation; only one patient had a normal electrocardiogram. The average cardiac size was 33 per cent greater than predicted. It was greater in the presence of auricular fibrillation than in patients with sinus rhythm.

These clinical changes were attended by slight further decreases in the maximal breathing and vital capacities. (Table III, Fig. 2.) The few patients with wheezing had maximal breathing capacities that were less than the average for the group. However, their air velocity indices and timed vital capacities were nearly normal, militating against the interpretation of undue airway obstruction.

There were no significant changes in the resting respiratory rate, minute ventilation, oxygen consumption or ventilatory equivalent. (Table II.) During exercise the ventilatory requirement was slightly larger than expected. The walking index and resting breathing reserve, which were 29 and 88 per cent, respectively, were significantly abnormal but were not commensurate with the growing disability. (Table III.)

There was further symmetrical reduction of the inspiratory capacity and expiratory reserve

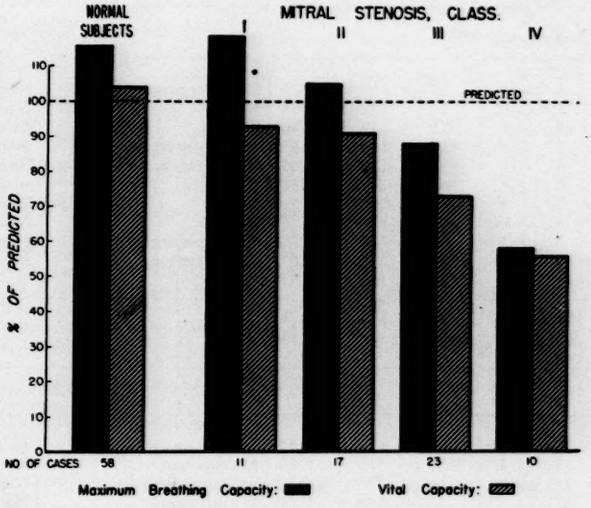

FIG. 2. Maximal breathing capacities and vital capacities expressed as per cent of the predicted normal for each group. Mean values of normal subjects and of patients with mitral stenosis are shown.

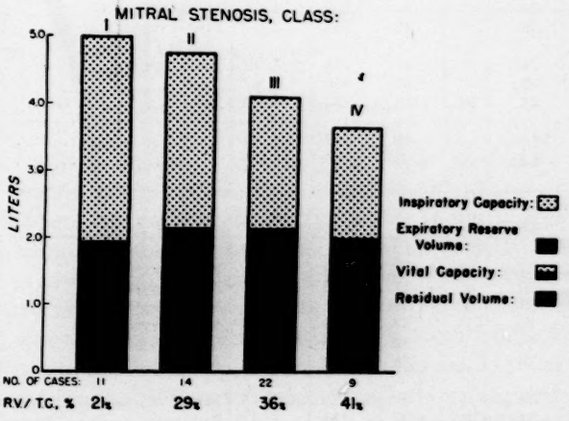

FIG. 3. The mean total lung capacity and its subdivisions, expressed in liters, and the ratio of residual volume to total lung capacity in patients with mitral stenosis.

volume. (Table II, Fig. 3.) Cardiac enlargement was considerably less among patients with normal total lung capacities than among those with reduced lung capacities. (Tables I and III.)

The residual volume continued to increase, becoming greater than predicted in all but two

TABLE I

PHYSICAL CHARACTERISTICS AND CLINICAL FEATURES OF SIXTY-TWO PATIENTS WITH MITRAL STENOSIS

Patient No.	Sex	Age	Height (cm.)	Body Surface Area (m^2)	Clinical Findings in Addition to Mitral Stenosis			
					Valvular Lesions	Abnormal Physical Findings	E.C.G.*	Teleroentgenogram: Per cent Cardiac Enlargement
					Functional Class I			
1.	F	16	164	1.78	Mitral regurg.	None	Normal	10
2.	M	19	170	1.71	None	None	Normal	0
3.	"	25	159	1.70	None	None	Normal	0
4.	"	20	160	1.63	Mitral regurg.	None	Normal	0
5.	"	32	173	2.05	Mitral regurg.	None	Normal	5
6.	"	42	180	1.88	None	None	Normal	0
7.	F	19	163	1.56	None	None	None	0
8.	M	17	178	1.76	None	None	Normal	0
9.	F	34	165	1.70	Mitral regurg.	None	Normal	0
10.	M	17	178	1.87	Mitral regurg.	None	Normal	10
11.	"	22	188	1.92	None	None	None	0
Mean	..	24	171	1.78	.....	.....	.....	2
S.D.	..	± 8	± 9	±0.14	.....	.....	.....	± 4
					Functional Class II			
12.	M	30	175	1.85	Mitral regurg.	Hepatomegaly	A.F.	35
13.	F	20	175	1.62	Mitral regurg.	None	Ab. P wave	20
14.	"	31	175	1.72	Mitral regurg.	None	Normal	10
15.	"	35	160	1.59	Mitral regurg.	None	A.F.	25
16.	"	15	160	1.15	Mitral regurg.	None	A.F.	20
17.	M	34	177	1.76	Mitral regurg.	None	A.F.	15
18.	"	34	180	2.05	Mitral regurg.	None	A.F.	20
19.	"	38	182	1.93	None	None	A.F.	35
20.	F	17	160	1.54	Mitral regurg.	None	Normal	10
21.	"	45	169	1.57	None	None	Inc., rt. B.B.B.	30
22.	M	25	186	1.87	Mitral regurg.	None	A.F. rt. V.E.	35
23.	F	21	168	1.64	Mitral regurg.	None	Normal	0
24.	"	28	160	1.67	Mitral regurg.	None	Normal	0
25.	"	33	161	1.57	Mitral regurg., aortic stenosis	None	A.F.	..
26.	"	37	158	1.80	Mitral regurg.	None	A.F.	25
27.	"	40	160	1.67	None	None	Shift. auric. pacemaker	20
28.	M	25	176	1.65	None	None	Normal	5
Mean	..	30	170	1.69	.....	.....	.....	19
S.D.	..	± 8	± 9	±0.20	.....	.....	.....	±12
					Functional Class III			
29.	M	57	189	1.95	Mitral regurg.	None	V.P.B., rt. V.E.	25
30.	"	37	173	1.81	Mitral regurg.	Rales, hepatomegaly	A.P.B., rt. V.E.	15
31.	F	30	156	1.48	Mitral regurg.	None	Rt. V.E.	30
32.	M	37	158	1.44	Mitral regurg.	Hepatomegaly	Normal	65
33.	"	32	188	2.04	Mitral regurg.	Hepatomegaly	A.F., rt. V.E.	Not measurable
34.	"	35	179	1.76	Mitral regurg.	Rhonchi, hepatomegaly	A.F., myocard. damage; dig. effect	35
35.	F	28	170	1.65	Mitral regurg.	None	Ab. P wave, rt. V.E.	25
36.	"	27	154	1.41	None	Hepatomegaly	A.F., V.P.B.	45
37.	M	42	184	1.93	None	None	A.F.	..
38.	F	29	166	1.57	None	Hepatomegaly	Ab. P wave; rt. V.E.	20
39.	"	38	156	1.48	None	None	Ab. P wave; myocard. damage	10
40.	"	41	156	1.37	Mitral regurg.	Wheezing	Rt. V.E., A.F.	10
41.	"	24	162	1.55	Mitral regurg.	None	A.F., rt. V.E., lt. V.E.	..
42.	M	36	177	1.67	Mitral regurg.	None	Ab. P. wave; rt. V.E.	55
43.	F	33	155	1.52	None	Rales	Ab. P wave; Inc. rt. B.B.B.	20
44.	M	37	184	1.97	Mitral regurg.	Hepatomegaly	A.F., rt. B.B.B.	45
45.	F	47	162	1.69	Mitral regurg.	Rhonchi, wheezing, dependent edema	Ab. P wave; dig. effect	10
46.	F	42	163	1.54	Mitral regurg.	Wheezing	Ab. P wave; inc. A-V B.	65
47.	"	42	157	1.57	None	Hepatomegaly	A.F.; myocard. damage	25

TABLE I (*Continued*)

Patient No.	Sex	Age	Height (cm.)	Body Surface Area (m^2)	Clinical Findings in Addition to Mitral Stenosis: Valvular Lesions	Abnormal Physical Findings	E.C.G.*	Teleroentgenogram: Per cent Cardiac Enlargement
48.	"	30	161	1.47	None	None	A.F.; V.P.B.	65
49.	M	29	180	1.75	Mitral regurg.	Hepatomegaly	A.F.; myocard. damage	50
50.	F	43	162	1.65	Mitral regurg.	Dependent edema	A.F.; myocard. damage	Not measurable
51.	"	22	170	1.54	None	None	Inc. A-V. B.; dig. effect	5
Mean	..	36	168	1.64	.....	.....	.....	 33
S.D.	..	± 8	± 12	±0.19	.....	.....	.....	..... ±20
					Functional Class IV			
52.	F	56	160	1.54	Mitral, aortic and tricuspid regurg.; aortic stenosis	Ascites, hepatomegaly	A.F.; dig. effect	55
53.	M	37	180	1.78	Mitral regurg.	Hepatomegaly	A.F.; dig. effect	40
54.	"	48	168	1.91	Mitral, aortic and tricuspid regurg.; aortic stenosis	Rt. hydrothorax, hepatomegaly, dependent edema	Inc. rt. B.B.B.; A.F.	55
55.	"	55	179	1.63	None	Rales	Inc. rt. B.B.B.; A.F.	10
56.	"	34	179	1.69	Mitral regurg.	Wheezing, hepatomegaly	.....	..
57.	"	47	173	1.73	Mitral and tricuspid regurg.	Rales, hepatomegaly	A.F.; rt. V.E., lt. V.E.	Not measurable
58.	F	45	147	1.56	Mitral regurg.	Lt. hydrothorax, hepatomegaly	A.F., rt. V.E.	
59.	M	35	188	2.28	Mitral and tricuspid regurg.	Wheezing, rt. hydrothorax, ascites, hepat., dependent edema	A.F., rt. V.E.; dig. effect	Not measurable
60.	F	65	160	1.67	Mitral, aortic and tricuspid regurg.; aortic stenosis	Ascites, hepatomegaly	A.F.; myocard. damage; dig. effect	65
61.	"	50	162	1.63	Mitral regurg.	Rales, rt. hydrothorax, ascites, hepatomegaly dependent edema	A.F.; inc. rt. B.B.B.	Not measurable
62.	"	39	160	1.44	Mitral and aortic regurg.	Rales, bilat. hydrothorax, hepatomegaly	A.F.; dig. effect	65
Mean	..	46	169	1.71	.....	.....	.....	49
S.D.	..	±10	± 12	±0.23	.....	.....	.....	±19

* Abbreviations:
A.F. = auricular fibrillation
Ab. = abnormal
Inc. rt. B.B.B. = incomplete right bundle branch block
V.E. = ventricular enlargement
Rt. V.E. = right ventricular enlargement
V.P.B. = ventricular premature beats
A.P.B. = auricular premature beats
Inc. A-V. B = incomplete auriculo-ventricular block

patients. (Table III.) As a result, the residual volume/total lung capacity ratio rose further. There was no impairment of gaseous distribution except in one patient, a forty-two year old woman whose pulmonary mixing index was 2.47 per cent. Her maximal breathing capacity and the fractions of her total vital capacity expelled per unit of time were normal; there was no clinical or fluoroscopic evidence of obstructive emphysema.

Class IV. The patients in this class were unable to perform even slight activity without discomfort. All of them had auricular fibrillation and signs of congestive circulatory failure. (Table I.) The average increase in transverse cardiac diameter was 49 per cent; the diameter could not be measured in three patients because of the presence of hydrothorax.

The maximal breathing capacity was reduced to 58 per cent of predicted. (Table III, Fig. 2.) As indicated previously, the predicted values are based on estimates of the body surface area. Because these estimates were artificially increased by edema fluid, the decreases in maximal breathing capacity were exaggerated when expressed in terms of deviations from the predicted normal. Patient No. 53 had a surprisingly high maximal ventilatory capacity which was 116 per cent of predicted. It was attributable, in part, to the vigorous treatment he was receiving prior to surgery for mitral stenosis. The upright vital capacity was reduced to 57 per cent but the fractions of this volume expelled per unit of time were only slightly affected. (Table II, Fig. 1.) Several patients in this group appeared to be too dyspneic to maintain a forced expiratory effort for more than two or three seconds. Consequently, the per-

centages of their vital capacity expelled per unit of time approached normal values. There were slight elevations of the mean resting respiratory rate, minute ventilation and ventilatory equivalent. (Table II.) Oxygen consumption remained unchanged and the tidal volume decreased slightly.

cent. The intrapulmonary mixing index remained within normal range in every patient.

ANALYSIS OF DATA

The statistical analyses of the data are contained in Table IV.

TABLE II

MEAN TIMED VITAL CAPACITIES, VENTILATION, OXYGEN UPTAKE AND LUNG VOLUMES IN MITRAL STENOSIS

	Functional Classification			
	I	II	III	IV
No. of patients	11	17	23	11
Mean age (yr.)	24 ± 8	30 ± 8	36 ± 8	46 ± 10
Vital capacity, % of total:				
3 Seconds	98 ± 3	94 ± 5	91 ± 8	89 ± 7
2 Seconds	95 ± 4	90 ± 6	84 ± 11	82 ± 10
1 Second	84 ± 6	75 ± 9	71 ± 12	69 ± 15
Resting respiratory rate	16 ± 4	14 ± 5	15 ± 3	19 ± 4
Resting tidal volume, ml./m²B.S.A	335 ± 75	435 ± 190	415 ± 100	325 ± 80
Resting ventilation, L./min./m²B.S.A	5515 ± 1705	5675 ± 915	5875 ± 1040	6045 ± 1350
Resting oxygen uptake, ml./min./m²B.S.A	145 ± 24	150 ± 20	155 ± 28	150 ± 25
Ventilatory equivalent	3.0 ± 0.6	3.0 ± 0.6	3.2 ± 0.8	3.4 ± 0.6
Inspiratory capacity (ml.)	3035	2600	1970	1625
Expiratory reserve (ml.)	885	820	625	520
Vital capacity (ml.)	3920	3425	2595	2145
Residual volume	1070	1325	1515	1505
Total lung capacity	4990	4750	4110	3645
$\frac{\text{Inspiratory capacity}}{\text{Vital capacity}} \times 100$	78 ± 4	76 ± 6	76 ± 6	76 ± 8

Six patients were unable to finish the mild exercise test. Among the remainder, the walking index rose sharply to 49 per cent, more as a result of the contracting maximal breathing capacity than an increase of the walking ventilation. The ventilatory requirement during effort was no greater than it had been in Class III. (Table III.) Fatigue and weakness were the limiting factors as often as dyspnea among the patients who could not complete the test. The resting breathing reserve was reduced to 79 per cent. (Table III.)

Further symmetrical reductions of the inspiratory capacity and expiratory reserve volumes (Table II) lowered the supine vital capacity to 60 per cent of predicted. The total lung capacity dropped to 73 per cent. (Table III.) The residual volume, although remaining greater than normal, was not so large as in Classes II and III. (Fig. 3.) The residual volume/total lung capacity ratio rose to 38 per

The clinical findings such as rales, hydrothorax and ascites were infrequent and tended to occur together. As a result, any interpretation of the ventilatory changes associated with these individual findings must remain tenuous. Two observations, however, are noteworthy:

1. The patients with hydrothorax showed greater reductions in maximal breathing, vital and total lung capacities than did the other members of the same functional class. In contrast to reports by others,[43] the residual volume was not excessively decreased.

2. The patients with ascites had more severe reductions in maximal breathing, vital and total lung capacities than did the others in the class. In addition, the residual volume was sharply reduced, suggesting an analogous behavior between ascites and pneumoperitoneum.[44] The effect of ascites upon ventilatory functions will be more thoroughly examined in a future report.[45]

TABLE III

MAXIMAL AND EXERCISE VENTILATION, INTRAPULMONARY MIXING INDICES AND LUNG VOLUMES EXPRESSED AS PER CENT OF PREDICTED

Patient No.	V.C. Upright % of Predicted	M.B.C. % of Predicted	Air Velocity Index	Breathing Reserve at Rest, %	Walking Ventil. L./min. m^2B.S.A.	Walking Index, %	V.C. Supine % of Predicted	Residual Volume % of Predicted	Total Lung Capacity % of Pred.	R.V. / T.L.C. × 100 %	Mixing Index % Alveolar Nitrogen
Mitral Stenosis, Functional Class I											
1.	82	100	1.2	92	13	20	90	112	95	24	0.55
2.	99	131	1.3	91	12	12	105	105	107	20	0.49
3.	88	123	1.4	93	9	10	91	76	88	17	0.75
4.	81	115	1.4	95	12	16	85	90	86	21	0.70
5.	79	104	1.3	94	..	..	82	108	88	24	0.34
6.	123	123	1.0	94	17	21	135	124	132	22	2.51
7.	89	111	1.2	95	10	14	93	95	93	20	0.91
8.	72	138	1.9	96	10	9	85	90	86	19	2.75
9.	117	130	1.1	94	9	13	120	132	122	22	0.48
10.	87	119	1.4	93	12	13	101	110	103	22	0.91
11.	101	113	1.1	96	10	12	105	121	108	22	1.16
Mean	93	119	1.3	94	11	14	99	105	101	21	1.05
S.D.	± 16	± 12	±0.2	± 2	± 2	± 4	± 16	± 18	± 15	± 2	±0.78
Mitral Stenosis, Functional Class II											
12.	68	83	1.2	91	15	26	...	...	...	..	....
13.	72	113	1.6	92	15	21	72	120	82	29	0.38
14.	103	114	1.1	92	10	15	106	183	121	30	0.57
15.	103	112	1.1	87	14	23	99	178	117	43	1.34
16.	75	71	0.9	87	11	23	...	...	...	..	....
17.	72	92	1.3	93	9	14	80	169	97	35	0.99
18.	122	100	0.8	91	8	11	121	153	128	24	0.38
19.	105	143	1.4	94	12	13	106	145	115	30	0.36
20.	91	108	1.2	92	15	21	97	115	101	23	0.45
21.	89	155	1.7	94	8	11	90	130	100	31	0.56
22.	85	93	1.1	91	..	..	97	103	98	21	1.11
23.	86	123	1.4	93	14	19	88	120	94	26	0.41
24.	106	101	1.0	93	12	20	112	134	111	23	0.57
25.	98	101	1.0	93	10	18	...	...	...	..	....
26.	91	84	0.9	90	..	..	96	128	104	29	0.65
27.	104	106	1.0	89	10	19	106	126	111	27	0.45
28.	78	94	1.2	92	10	14	85	144	97	30	1.13
Mean	91	105	1.2	91	12	18	97	139	105	29	0.67
S.D.	± 15	±20	±0.3	± 2	± 3	± 5	± 13	± 24	± 12	± 6	±0.33

TABLE III (*Continued*)

Patient No.	V.C. Upright % of Predicted	M.B.C. % of Predicted	Air Velocity Index	Breathing Reserve at Rest, %	Walking Ventil. L./min. m^2B.S.A.	Walking Index, %	V.C. Supine % of Predicted	Residual Volume % of Predicted	Total Lung Capacity % of Pred.	R.V./T.L.C. × 100 %	Mixing Index % Alveolar Nitrogen
Mitral Stenosis, Functional Class III											
29.	94	88	0.9	92	..	..	106	137	116	37	0.70
30.	65	57	0.9	87	13	34	59	197	91	51	0.95
31.	71	91	1.3	87	11	21	72	120	81	30	0.44
32.	63	77	1.2	85	22	43	63	105	73	34	0.33
33.	62	73	1.2	84	..	..	69	193	94	41	1.14
34.	78	86	1.1	89	16	27	60	127	76	39	1.28
35.	80	116	1.5	84	21	32	79	270	117	46	1.07
36.	52	83	1.6	86	11	22	61	131	75	35	0.44
37.	71	90	1.3	89	..	..	85	137	97	33	0.42
38.	92	156	1.7	96	16	19	111	162	121	27	1.44
39.	114	101	0.9	91	21	39	123	133	123	21	0.72
40.	70	70	1.0	..	..	..	...	...	...	..	....
41.	67	59	0.9	84	..	..	54	83	60	28	0.51
42.	82	97	1.2	93	..	..	79	191	105	43	1.04
43.	67	120	1.8	91	14	20	69	97	74	26	0.42
44.	79	94	1.2	92	..	..	91	122	98	29	0.46
45.	86	61	0.7	81	11	36	75	226	110	48	1.45
46.	60	101	1.7	89	14	26	71	159	92	41	2.47
47.	79	125	1.6	91	13	20	74	144	91	37	0.61
48.	47	88	1.9	90	12	23	51	169	74	46	0.94
49.	55	42	0.8	81	12	28	52	136	69	40	0.71
50.	72	60	0.8	79	14	46	67	170	88	39	0.84
51.	69	85	1.2	92	15	29	82	125	91	28	1.28
Mean	73	88	1.2	88	15	29	75	152	92	36	1.03
S.D.	± 15	± 25	±0.3	± 4	± 3	± 8	± 19	± 48	± 18	± 8	±0.96
Mitral Stenosis, Functional Class IV											
52.	34	49	1.4	65	..	..	61	97	72	42	1.12
53.	81	116	1.4	91	..	..	86	133	97	32	0.80
54.	56	44	0.8	..	..	..	...	...	...	..	....
55.	70	84	1.2	86	..	..	70	140	91	47	1.32
56.	...	...	...	..	..	..	42	138	61	42	1.12
57.	70	84	1.2	90	14	28	74	185	100	43	0.70
58.	48	26	0.5	62	..	..	50	172	73	51	0.97
59.	45	36	0.8	81	11	43	51	106	64	39	0.87
60.	70	44	0.6	78	15	49	84	97	88	35	0.98
61.	46	43	0.9	73	14	70	...	...	...	..	....
62.	49	53	1.1	81	15	54	42	93	54	40	0.64
Mean	57	58	1.0	79	14	49	62	129	78	41	0.95
S.D.	± 15	± 28	±0.3	±10	± 2	±15	± 17	± 34	± 13	± 6	±0.20

COMPARISON OF VENTILATORY INSUFFICIENCY IN MITRAL STENOSIS AND PRIMARY PULMONARY DISEASE

Many of the respiratory symptoms in mitral stenosis are comparable in type and degree to those experienced by patients with primary pulmonary disease. To bring the ventilatory defect of mitral stenosis into proper perspective the data of patients severely disabled by mitral stenosis have been compared with those of patients equally disabled by primary pulmonary disease. (Table v.) Comparison has been confined to those with marked incapacity included in functional Classes III and IV.

There is no difficulty in finding patients who

TABLE IV

RELATIONSHIPS OF VENTILATORY STUDIES TO FUNCTIONAL CLASSIFICATION AND CARDIAC ENLARGEMENT

	Functional Classification		Cardiac Enlargement	
	Variance Ratio*	Level of Significance	Coefficient of Correlation	Level of Significance
Vital capacity, % of total 3 seconds	4.95	0.01	.....	....
Vital capacity, upright, % of predicted	14.83	0.01	−0.60	0.01
Maximal breathing capacity, % of predicted	14.61	0.01	−0.54	0.01
Air velocity index	2.00	0.02	+0.16	0.02
Breathing reserve, resting	17.50	0.01	−0.57	0.01
Walking index	28.51	0.01	+0.63	0.01
Vital capacity, supine, % of predicted	12.50	0.01	−0.59	0.01
Residual volume, % of predicted	4.84	0.01	+0.15	0.01
Total lung capacity, % of predicted	6.55	0.01	−0.45	0.01
$\frac{\text{R.V.}}{\text{T.L.C.}} \times 100$	21.55	0.01	+0.59	0.01
Tidal volume, ml. m^2B.S.A	2.60	0.02	.....	....
Resting ventilation, L./min./m^2B.S.A	1.81	0.02	.....	....

* Compares the greater variance among functional classes to the lesser variance within each class.

TABLE V

A COMPARISON OF VENTILATORY FUNCTIONS AMONG PATIENTS SEVERELY DISABLED BY MITRAL STENOSIS OBSTRUCTIVE AND RESTRICTIVE PULMONARY DISEASE

	Normal Values	Patients Severely Disabled by:		
		Mitral Stenosis	Restrictive Insufficiency	Obstructive Insufficiency
No. of patients	.....	37	13	47
Vital capacity, % of total				
3 Seconds	97	90	97	64
2 Seconds	93	82	93	51
1 Second	87	68	82	39
Vital capacity, upright, % of predicted	100	68	39	66
Maximal breathing capacity, % of predicted	100	79	46	36
Air velocity index	8–1.2	1.2	1.1	0.5
Walking index	10–20	34	48	60
Residual volume % of predicted	100	145	60	257
Total lung capacity, % of predicted	100	88	46	119
R.V./T.L.C. × 100	20–30	38	32	62
Mixing index				
% alveolar nitrogen	<1.5	1.04	0.99	6.40

are severely disabled by "obstructive" ventilatory insufficiency; the most common clinical cause of this defect is pulmonary emphysema. Functional changes are usually attributed to destruction of pulmonary elastic tissue and to increased air flow and tissue resistance. Usually, the total lung capacity remains unchanged, the

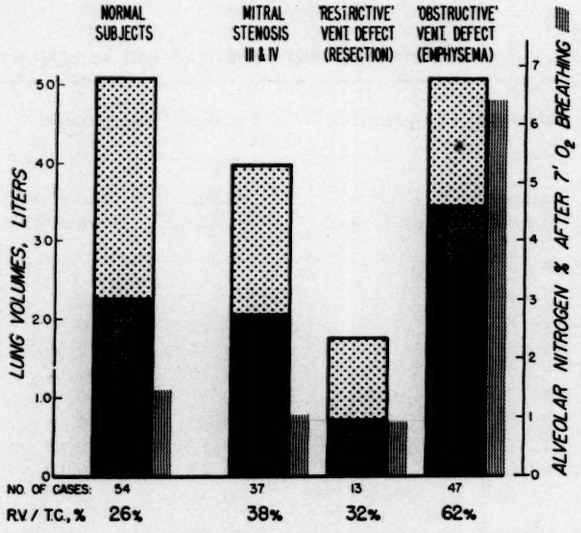
NORMAL SUBJECTS
MITRAL STENOSIS III & IV
'RESTRICTIVE' VENT. DEFECT (RESECTION)
'OBSTRUCTIVE' VENT. DEFECT (EMPHYSEMA)
LUNG VOLUMES, LITERS
ALVEOLAR NITROGEN % AFTER 7' O_2 BREATHING
NO. OF CASES: 54 37 13 47
RV / T.C., % 26% 38% 32% 62%

FIG. 4. The means of total lung capacity and its subdivisions, the ratio of residual volume to total lung capacity and the intrapulmonary mixing index of normal subjects, of patients severely disabled by mitral stenosis (Classes III and IV), and of patients with primary pulmonary disease with similar disability due to restrictive and obstructive ventilatory insufficiency. The code for the subdivisions of the lung volume is the same as in Figure 3.

whom were severely disabled. The vital capacity, determined in the supine position, was reduced by one-third in both mitral stenosis and emphysema, and by two-thirds in restrictive insufficiency. The total lung capacity was lowered only slightly in mitral stenosis, unaffected in emphysema and reduced to less than one-half of

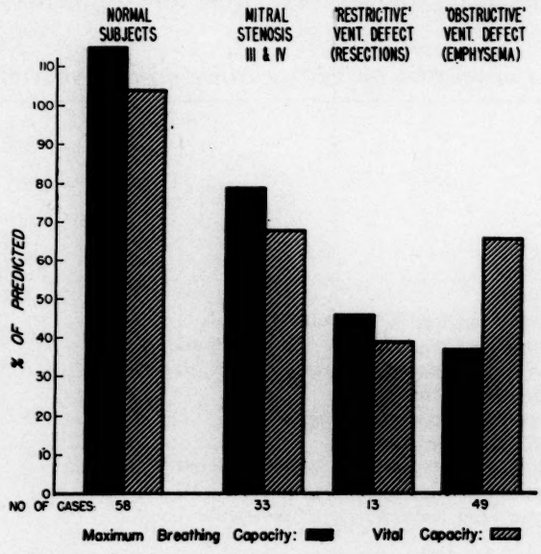

FIG. 5. Mean maximal breathing capacities and vital capacities, expressed as per cent of the predicted, of normal subjects, of patients with severely limited activity due to mitral stenosis (Classes III and IV) and of patients with primary pulmonary disease with similarly limited activity due to restrictive or obstructive ventilatory insufficiency.

interrelationships of its subdivisions are altered, the maximal respiratory velocity is decreased and intrapulmonary mixing is impaired.[44,46]

"Restrictive" ventilatory insufficiency is due to anatomic changes of the chest wall, pleural space or pulmonary parenchyma which reduce the amount of available aerated tissue.[34] Such patients are rarely severely limited in their activity; only thirteen qualifying patients were found in our files. Most of these had been treated with bilateral collapse for pulmonary tuberculosis; a few had undergone pneumonectomy and additional treatment for parenchymal disease of the remaining lung.

In Figure 4 and Table v the lung compartments of fifty-four normal volunteers were compared with those of thirty-seven patients having mitral stenosis, with thirteen patients having restrictive ventilatory insufficiency and with forty-seven patients having obstructive emphysema, all of predicted in restrictive disease. In both mitral stenosis and emphysema the residual volume was greater than predicted, the increase being considerably more in the latter group. The residual volume/total lung capacity ratio was correspondingly larger in emphysema. In restrictive disease the residual volume was reduced almost equally with the other lung compartments. Intrapulmonary gaseous distribution, as measured by the pulmonary mixing index, was adequate in both mitral stenosis and restrictive disorders, but grossly impaired in emphysema.

The maximal breathing capacity has been justly considered as one of the most reliable indices of ventilatory insufficiency in primary pulmonary disease. Among such patients in our study, disability was not severe until the maximal breathing capacity was reduced to less than one-half of normal. (Fig. 5.) Rare exceptions

were encountered among patients with diffuse granulomatous diseases in whom the maximal breathing capacity and other conventional ventilatory functions were little disturbed. In mitral stenosis, by contrast, disability was often severe despite a maximal breathing capacity that was three-fourths of normal.

patients with pulmonary disease usually are not severely dyspneic until their walking indices are approximately 50 per cent or more.[41] Such high values prevailed among patients incapacitated by pulmonary disease but not among those with mitral stenosis, in whom the mean walking index was only 34 per cent. Figure 6 illustrates

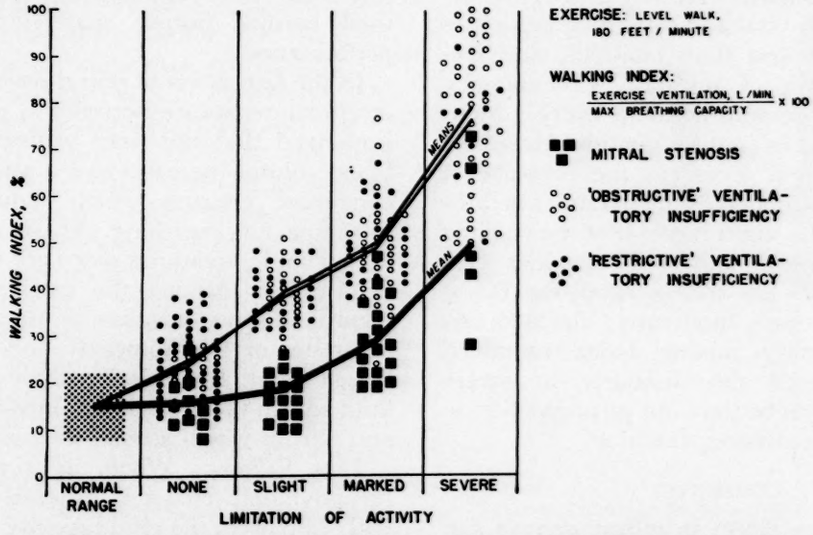

FIG. 6. The walking dyspnea index (walking ventilation ×100/maximal breathing capacity) of normal subjects and of patients with varying limitation of activity due to mitral stenosis, obstructive ventilatory insufficiency and restrictive ventilatory insufficiency.

In pulmonary emphysema the air velocity index was only 0.5 (Table v), reflecting a disproportionately greater reduction of the maximal breathing capacity than of the vital capacity. (Fig. 5.) Patients with either mitral stenosis or restrictive ventilatory insufficiency had nearly equal reductions so that their air velocity indices remained within normal limits. The changes in maximal breathing capacity in restrictive disease were due almost entirely to a diminished maximal stroke volume without any measurable reduction in the speed of exchange; the timed vital capacity remained normal. In patients with mitral stenosis the moderate fall in the maximal breathing capacity appeared to be due largely to changes in stroke volume although the maximal flow rate, as measured by the timed vital capacity, was slightly diminished. In emphysema, the maximal breathing capacity and timed vital capacities were greatly reduced, indicating an excessive slowing of the rate of air flow.

The relationship between the maximal breathing capacity and walking ventilation is expressed by the walking index. Warring has shown that this point. Our patients with mitral stenosis and a large number of patients with primary pulmonary disease were classified according to their stage of disability and the walking indices were plotted for each group. The control group required about 8 to 22 per cent of its maximal breathing capacity for the standard exercise. The patients with pulmonary disease who had slight limitation of activity showed a definite elevation of the walking index, whereas the patients similarly limited by mitral stenosis had normal values. This discrepancy became more striking as disability increased. Severely disabled patients with pulmonary disorders required approximately one-half of their best ventilatory effort for the standard exercise while those equally disabled by mitral stenosis required only approximately one-third.

The limited activity of patients with obstructive or restrictive pulmonary disease was well mirrored by changes in the pulmonary functional studies. These patients did not become severely disabled until their maximal breathing capacity was less than one-half of

normal and until more than one-half of this residuum was required during mild exercise. Patients with emphysema were usually not severely incapacitated before the residual volume occupied more than 50 per cent of the total lung capacity and the intrapulmonary mixing index was more than twice the normal value. Patients with restrictive disease were not greatly handicapped until their vital and total lung capacities were reduced to less than one-half, and frequently one-third, of normal. A ventilatory defect could be demonstrated in every patient severely disabled by mitral stenosis. However, disability was often severe in the presence of only moderate reduction of the maximal breathing capacity and a slight increase of the walking index. The total lung and vital capacities were often only slightly less than normal, the R.V./T.L.C. ratio was only moderately elevated and the intrapulmonary mixing index remained unchanged. Hence the disability in severe mitral stenosis was entirely out of proportion to the changes in ventilatory function.

COMMENTS

The ventilatory defect in mitral stenosis can best be understood by a consideration of the known hemodynamic changes. As mitral stenosis increases in severity, with or without varying degrees of regurgitation, the pressure within the left auricle must rise to insure adequate flow through the stenotic valve. This rise is transmitted retrogressively through the pulmonary venous system to the arterial side of the pulmonary circulation.[47–55] In turn, the pulmonary arterial hypertension is augmented by local arteriolar constriction which reduces the vascular capacity; some of the organic vascular changes noted at postmortem study may contribute to the increase in pressure.[56,57] Hypertension probably stiffens the lung, impairing distensibility and provoking a necessary increase in the muscular work required for respiration. Hemosiderosis, which has been observed after repeated hemoptyses,[58] may add to the mechanical defect. There appears to be no measurable increase in pulmonary blood volume at rest during the compensated stage of the disease;[59–61] apparently "congestion" is not yet a factor in determining the ventilatory changes.

During effort there is a greater demand on cardiac output and the vascular pressures must rise to increase flow past the stenotic valve.[47,54,55,62,63] Ventricular filling which is delayed by the defective valve probably occurs at a virtually uniform rate throughout diastole.[64] Under these circumstances an excessive increase in pulse rate produces a reduction in flow through the stenosed mitral valve and an actual fall in minute output.[55,62] Consequently, the energy required to ventilate the lung is magnified at a time when the reductions in stroke volume and total cardiac output may impair muscular performance.

In the late stages of mitral disease pulmonary arteriolar resistance becomes so great and is so prolonged that the right ventricle fails. Total blood volume increases and is attended by local congestive changes which reduce the space available for breathing. These encroachments on available breathing space are either extrinsic or intrinsic. Among the extrinsic factors are pleural effusion, elevation of the diaphragm due to ascites or hepatomegaly and a greatly enlarged heart. Intrinsically, there is retention of fluid within the alveoli and inter-alveolar tissues and fibrosis which attends long-standing edema.

Lung Volumes. When, as a result of these hemodynamic changes, distensibility is sufficiently impaired, the vital capacity decreases. The reductions in the inspiratory capacity and expiratory reserve volumes in this study have been symmetrical throughout all stages of disability, although previous investigators have found predominant changes in one or the other volume.[3,4,7] As stated previously, our method of summing the largest of several inspiratory capacity and expiratory reserve volumes tends to enlarge the latter value. Before the stage of congestive circulatory failure the total lung capacity is unchanged or may be slightly decreased. The decrease, when it occurs, probably reflects both impaired distensibility and increasing cardiac size, the latter due chiefly to auricular enlargement. When signs of congestion occur, all divisions of the lung capacity are reduced below their immediately antecedent values because of vascular congestion and its sequelae. (Fig. 7.) The nature and severity of the congestive changes determine whether the residual volume falls below the predicted value; it may become significantly reduced in the presence of ascites. Cardiac enlargement, which now embodies a large ventricular component, contributes to most of these changes.

Dynamic Exchange. The maximal breathing capacity depends upon two factors: the maximal tidal volume and the rapidity with which this

volume can be exchanged. Reduction in the largest stroke volume is reflected by analogous changes in the vital capacity. A reduction in the rapidity of air flow may be due to increased resistance offered by the tracheobronchial tree or to increased tissue resistance. In mitral stenosis there is a decrease in maximal tidal volume but no large increase in total resistance when measured by these studies: the vital and maximal breathing capacities are equally reduced and.the maximal expiratory effort is only slightly delayed. Surprisingly, this is also true of the few patients who have wheezing and rales at the time of study. More direct measurement of the mechanical properties of the lung in mitral stenosis have demonstrated an increase in pulmonary resistance[65] which is less severe than that encountered in obstructive emphysema.[66] Another factor which aggravates the reduction in maximal ventilatory capacity, particularly in the advanced stages of cardiac failure, is muscular fatigue.

Resting Ventilation. The trends in ventilation at rest are difficult to evaluate. The respiratory rate, minute ventilation and ventilatory equivalent do gradually increase from Classes II through IV while the tidal volume decreases. These increases may have been minimized by the use of high oxygen mixtures during closed spirometry. It is probable that several of the excessive values observed among asymptomatic patients were related to anxiety and poor relaxation. Generally, each patient was studied on only one occasion and it is likely that many of them were not in a basal state.[67] On the basis of this work it is not possible to state whether resting hyperventilation is the earliest ventilatory change in mitral stenosis.

Normally, the force required to distend the lung during quiet breathing is small when measured by the static intrapleural pressure.[68–70] As the lung stiffens this force must be expected to increase if a constant tidal volume is to be maintained. The decrease in tidal volume which has been frequently described in cardiac disease may therefore represent an energy-saving adjustment. However, as this volume diminishes, less air traverses the tracheobronchial dead space with each breath[11,13,14] and, unless there is an increase in the respiratory rate, gaseous exchange becomes inadequate. The maintenance of effective alveolar ventilation ultimately depends on the balance established between the changing tidal volume and respiratory rate. An increase in the activity of the Hering-Breuer reflex, attending pulmonary rigidity, has been considered the mechanism by which these adjustments are made.[9,10,25] It is of interest, in the present study that, if a constant "dead space" of 150 ml. is assumed for each patient, the mean effective alveolar ventilation is maintained despite increasing disability.

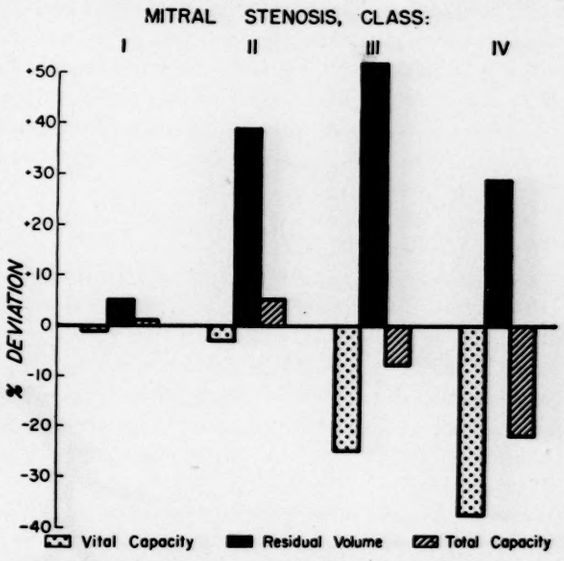

FIG. 7. The average per cent deviation from the predicted vital capacity, residual volume and total lung capacity in patients with mitral stenosis.

The ventilatory equivalent for oxygen has been considered a useful and accurate index of the severity of cardiac disease.[5,16–18] We have found it of little value in either cardiac or pulmonary disease when this equivalent is calculated from a spirometric tracing. Patients who hyperventilate because of anxiety or poor relaxation have an increase in minute ventilation that exceeds their increased oxygen consumption. The result is an elevated ventilatory equivalent occurring independently of the underlying disease. In addition, the spirometer and its valves offer resistance to breathing and may cause a gradual elevation of the pulmonary resting or mid-position; the elevation may be mistakenly interpreted as representing an increase in oxygen consumption. In general, this artefact is more prevalent among dyspneic patients.

Intrapulmonary Mixing. Despite the progressive increase of the R.V./T.L.C. ratio there is no discernible defect in the distribution of inspired gas. Nearly all of the nitrogen within the lung is removed after seven minutes of oxygen

breathing. The residual alveolar nitrogen or intrapulmonary mixing index remains normal.

Breathing Reserve. The breathing reserve at rest decreases while the walking index increases with disability. However, the latter increase, at least in Classes II and III, is not commensurate with symptoms. Many patients complain mainly of weakness and fatigue and have muscular aching in their chest and legs. Not uncommonly they discontinue exercise because of "shortness of breath," yet their walking minute ventilation and, infrequently, respiratory rate may be within normal range.

Clinical Significance of Ventilatory Studies in Mitral Stenosis. Whereas the study of ventilatory function is of established value in estimating the degree of disability due to pulmonary disease, it is not as rewarding when applied to patients with mitral stenosis. Here the changes in function before the onset of congestive failure are only slight and disability is out of proportion to observed alterations in pulmonary function. The severity of the disease may be estimated more accurately clinically and perhaps by direct studies of the cardiovascular system.

Clinically, the studies are important for evaluating patients who have both mitral valvular and primary pulmonary disease. This applies particularly to patients with complicating bronchial asthma or pulmonary emphysema who are to be evaluated for mitral valvuloplasty. If the relative contribution of the two lesions to the disability can be assessed, it is possible to predict, within limits, the extent of improvement that can be expected after operation. Having shown in our present study that mitral stenosis alone, irrespective of the severity of the disease, does not cause a marked obstructive defect, elevation of the pulmonary mid-position or defective distribution of gases, the extent of coexisting asthma or emphysema can be determined. The present study may also serve as a baseline for evaluation of patients for surgery for pulmonary tuberculosis or bronchogenic tumors who have complicating mitral stenosis. Bronchospirometry has been of clinical value in some patients with mitral stenosis for whom mitral surgery was planned but who had had a previous pleural effusion with poor re-expansion of the right lung.[71]

SUMMARY AND CONCLUSIONS

Pulmonary functional studies were performed in sixty-two patients with rheumatic heart disease in whom mitral stenosis was the predominant valvular lesion. The patients were classified according to the New York Heart Association criteria for functional limitation.

Patients with asymptomatic mitral stenosis had normal ventilatory functions except for occasional increases in resting minute ventilation and ventilatory equivalents. As symptoms appeared and progressed the following changes were noted:

1. There were gradual reductions in maximal breathing capacity and total vital capacity. The timed capacities were not greatly reduced.
2. Resting minute ventilation, respiratory rate and ventilatory equivalents rose slightly, while tidal volumes decreased. The calculated mean effective alveolar ventilation was maintained throughout all stages of disability.
3. The breathing reserve at rest and the walking index were not much affected until disability was severe. Patients not infrequently complained of weakness, fatigue or dyspnea during exercise without showing diminished breathing reserve or increased dyspnea indices.
4. There were symmetrical decreases of inspiratory capacity and expiratory reserve volumes. The residual volume rose early, largely at the expense of the expiratory reserve. Total lung capacities were not reduced until the advent of congestive circulatory failure; at that stage all divisions of the lung volume were diminished.
5. Cardiac enlargement, acute and chronic pulmonary edema, pleural effusion, ascites and hepatomegaly were of varying importance in reducing the lung volume compartments.
6. There was no gross impairment of the distribution of inspired gas within the lungs.

The relationship of altered ventilation to hemodynamic changes is discussed. The initial findings were largely ascribed to pulmonary rigidity attending hypertension, and the later findings to encroachments upon parenchymal tissue by both extrinsic and intrinsic congestive changes.

The ventilatory defect was not considered a useful quantitative index of disability except in far advanced disease. Pulmonary functional changes were compared to those occurring in primary diseases; in the latter diseases the defects more closely reflected disability.

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Review

Occlusive Auricular Thrombi*

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THE occurrence of ball-valve thrombi in the heart has been known for many years.[1] Recent advances in the field of cardiac surgery and angiography have suggested the possibility of operative treatment of these cases[2] and make further understanding of the physiologic mechanisms of this lesion desirable.

Without a definitive history it is frequently impossible to evaluate the findings at autopsy. Even when the complete clinical course is known, the pathologic correlation remains largely subjective and analysis of the mode of death in the presence of other significant factors (e.g., heart failure, visceral infarction, severe infection, bacterial endocarditis, cardiac arrhythmias, etc.) is particularly difficult.[9c,g]

TABLE I

Author	Autopsies (No.)	Rheumatic Heart Disease		Ball or Mass Thrombi		
		(No.)	(%)	(No.)	Autopsies (%)	RHD—(%)
Cleland[6]	3,000	....	...	1	0.03	....
Garvin[7]	6,285	156*	2.5	3	0.05	1.9
Evans & Benson[8]	3,083	46†	1.5	6	0.19	13.4
Wallach, Lukash & Angrist[5]	8,676	509	5.9	16	0.18	3.1

* Rheumatic heart disease is principal or contributory cause of death.
† Cases of mitral stenosis.

The total number of cases is somewhat difficult to ascertain because of variation in the criteria used by different authors for selecting these cases, depending on whether the thrombi are free, pedunculated or broadly attached, with consequent differences in terminology. Since the only factor of clinical significance is the presence of obstruction to the blood flow (usually through the orifice of the mitral valve) there is no advantage in maintaining artificial and rigid criteria which have been arbitrarily established.[3]

Furthermore, many cases have been mentioned casually in the literature dealing with related subjects with no description of the clinical and pathologic findings in these patients.[4] Numerous examples have probably remained unreported because of the absence of typical clinical or pathologic findings. If these latter cases were included in the literature, underestimation of the difficulties in making this diagnosis clinically would be avoided.

In a series of 8,676 consecutive autopsies performed at Queens General Hospital from 1936 to 1950 inclusive, 509 (5.9 per cent) were considered to show rheumatic valvular involvement. The selection of these cases has been previously described.[5] Seventy-two instances of minimal rheumatic involvement and 103 examples of calcific aortic stenosis were excluded.

Of these 509 cases sixteen were considered by the prosectors to represent massive or obstructing auricular thrombi. In eight instances the auricular thrombi were thought to be the immediate cause of death. These figures are compared to previous reported series in Table I.

In a review of the literature up to 1948 Evans and Benson[8] collected forty-six cases of mass thrombus and added six of their own. They compared the clinical aspects of these cases with twenty-seven reported cases of left auricular tumor (twenty-one with myxoma, five with

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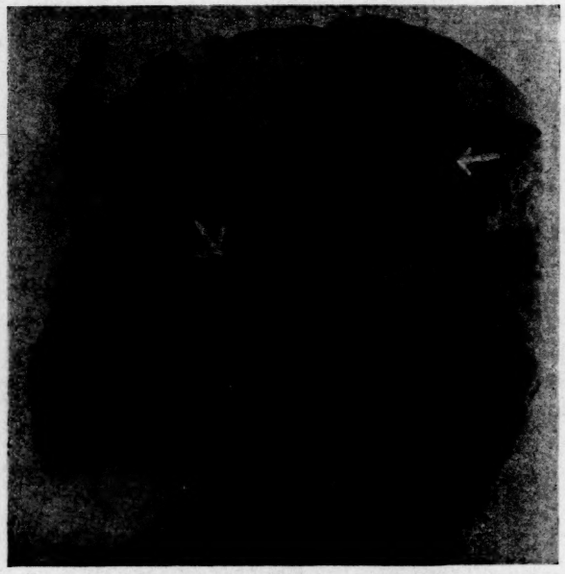


FIG. 1. Shows an hour-glass thrombus 4 cm. in length and 3 cm. in its widest diameter jammed into the mitral orifice. The thrombus must have been lodged in the mitral orifice for a considerable period of time in order for the accretion of the inferior portion of the thrombus to occur within the cavity of the ventricle. A free globular thrombus 2 cm.. in diameter is also seen in the left auricle (Case 1).

sarcoma and one with fibroma). They emphasized the following symptoms: Dyspnea was present in cases of tumor and of thrombus but in the latter it was frequently due to the associated mitral stenosis. Heart failure was of variable severity but was more rapidly progressive from the time of onset of symptoms in cases of tumor. Giddiness and syncope were thought to be more frequent in cases of tumor or thrombus than in cases of heart disease in general. Auricular fibrillation was found in thirty-eight previous cases and five of their own six cases of thrombus and was noted in four cases with tumor. Peripheral vascular phenomena were noted in twelve of the fifty-two cases with thrombi but were not definitely attributable to the tumor mass in cases with tumor. Cardiac murmurs were usually those of mitral stenosis but the thrombus may occasionally alter them; in the presence of tumor the occurrence and type of murmur was variable. Sudden death occurred in seven of the fifty-two cases with thrombus and in five of the cases with tumor. Postural effects were detected in five of the twenty-seven cases of tumor but were not noted in cases of thrombi. These authors emphasized the increased frequency of cardiac pain (ischemic) in those cases of mitral stenosis associated with a mass thrombus of the left auricle as contrasted to uncomplicated cases of mitral stenosis.

A review of American and British literature since 1948 has revealed several additional case reports.[9] The sixteen cases in the present series are briefly summarized in Table II. The clinical findings in these patients gave no clue to the presence of occlusive auricular thrombi, using the criteria which have been emphasized in the literature. The course of these patients was similar to that noted in comparable patients in whom these thrombi were absent, or was attributable to the presence of complicating factors (e.g., cerebral, visceral or peripheral embolization, intercurrent infection or superimposed coronary artery disease).

COMMENTS

From a study of the present cases and a review of many of the cases previously reported, it is difficult to concur in the usual explanation that the mode of death is the occurrence of a ball-valve mechanism or of a large auricular thrombus obstructing the mitral valve. It is suggested that the significant factor in any of these cases is a diminution of blood flowing into the left ventricle and consequently of diminished left ventricular output. This may be due to three possible mechanisms: (1) Obstruction of the mitral valve orifice itself by a ball-valve or mass thrombus; (2) filling of most of the left auricle by thrombus which acts as a space-occupying tumor, producing a reduction in the amount of blood which can be present in this chamber at any one time; (3) partial or complete occlusion of some of the pulmonary veins by thrombus in the left auricle with a resultant decrease in the amount of blood entering the left auricle[4b] (usually associated with 2).

Although any of these mechanisms may occur, it is postulated that the second mechanism, frequently associated with the third (Figs. 2 and 3), is the most common manner in which these thrombi attain significance, i.e., by acting as space-occupying tumors with a consequent diminution in blood flow through the left auricle. Physiologically, this is equivalent to further narrowing of the mitral orifice without altering the actual degree of anatomic obstruction and thus accounts for the symptoms of diminished cardiac output (dizziness and syncope, peripheral vascular phenomena, ischemic cardiac pain, progressive heart failure). The

TABLE II

Case*	Age and Sex	Cardiac Rhythm†	Infarcts‡	Heart Weight (gm.)	Valves§	Description of Thrombi**
1	24, F	RSR	L,K	450	MS-4+ AS-1+	Hour-glass thrombus jammed into mitral orifice; free globular thrombus 2 cm. in diameter in left auricle; thrombi in both appendages (Fig. 1)
2	47, M	AF	B	850	MS-4+	Left auricle almost entirely filled by thrombus which blocks off 3 of the pulmonary veins (Fig. 2)
3	48, M	AF	L	Markedly enlarged	MS-4+ AS-2+	Adherent thrombus extended to mitral valve; partial occlusion of pulmonary veins (Fig. 3)
4	52, M	AF	K, left brachial	Greatly enlarged	MS-4+ AS-4+ TS-1+	Round thrombus 6 × 4 × 4 cm. presumably free; small thrombus attached to wall of left auricle; (Fig. 4)
5	47, F	AF	L,K,S	400	MS-4+ AS-2+	Massive thrombus occluding mitral valve and filling left auricle; thrombus in right auricle (Fig. 5)
6	63, M	AF	K,S	650	MS-4+ AS-2+	Clot 4 cm. in diameter attached by broad base to anterior and posterior auricular wall 2 cm. above mitral ring
7	40, F	AF	L,K,S	510	MS-4+ AS-4+	Free thrombus 2.5 cm. in size; also small thrombus in right auricle
8	62, F	AF	None	720	MS-4+ AS-4+ TS-3+	Globular thrombus 5 cm. in diameter adherent to one wall, extending into right pulmonary vein where it was adherent
9	38, F	AF	None	Moderately dilated	MS-4+ AS-2+	Huge thrombus almost filled left auricle and extends into opening of mitral valve completely filling it; adherent at MacCallum's site and appendage
10	52, F	AF	K,S,B	260	MS-4+	Ball-like thrombus 3 cm. in diameter
11	67, F	AF	None	680	MS-4+ AS-2+ TS-1+	Large mural thrombus filled almost all of left auricle
12	76, F	AF	B	450	MS-3+	Large mural thrombus occupied one-third of left auricle and had a ball-valve effect
13	43, M	AF	L,K	780	MS-4+ AS-3+	Right auricle contained large ball-valve thrombus on small pedicle; organizing thrombus left appendage
14	41, F	?	L	475	MS-4+ AS-2+ TS-3+	Large ball-valve thrombus 5 cm. in diameter attached anteriorly
15	41, F	AF	B,K	700	MS-4+ AS-2+	Thrombus 8 × 10 cm. in diameter occluded left auricle
16	37, F	AF	K,S	420	MS-4+	Entire left auricle filled with large relatively fresh thrombus totaling about 150 cc.; underlying old thrombotic material; small thrombus right appendage

* All patients white.

† AF = Auricular fibrillation; RSR = regular sinus rhythm.

‡ L = Lung; K = kidney; S = spleen; B = brain.

§ MS = Mitral stenosis; AS = aortic stenosis; TS = tricuspid stenosis; 1+ to 4+ = grading of valvular distortion with 1+ least severe and 4+ most severe.

** All thrombi in left auricle unless otherwise described.

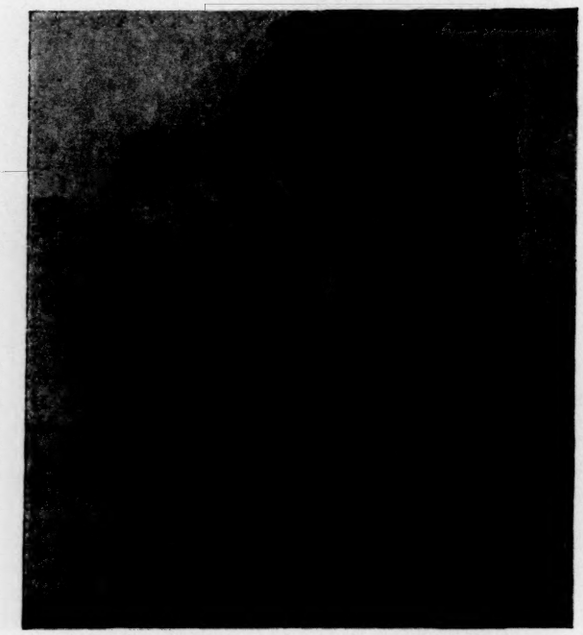


FIG. 2. Shows the left auricle almost entirely filled by thrombus which has occluded three of the pulmonary veins (Case 2).

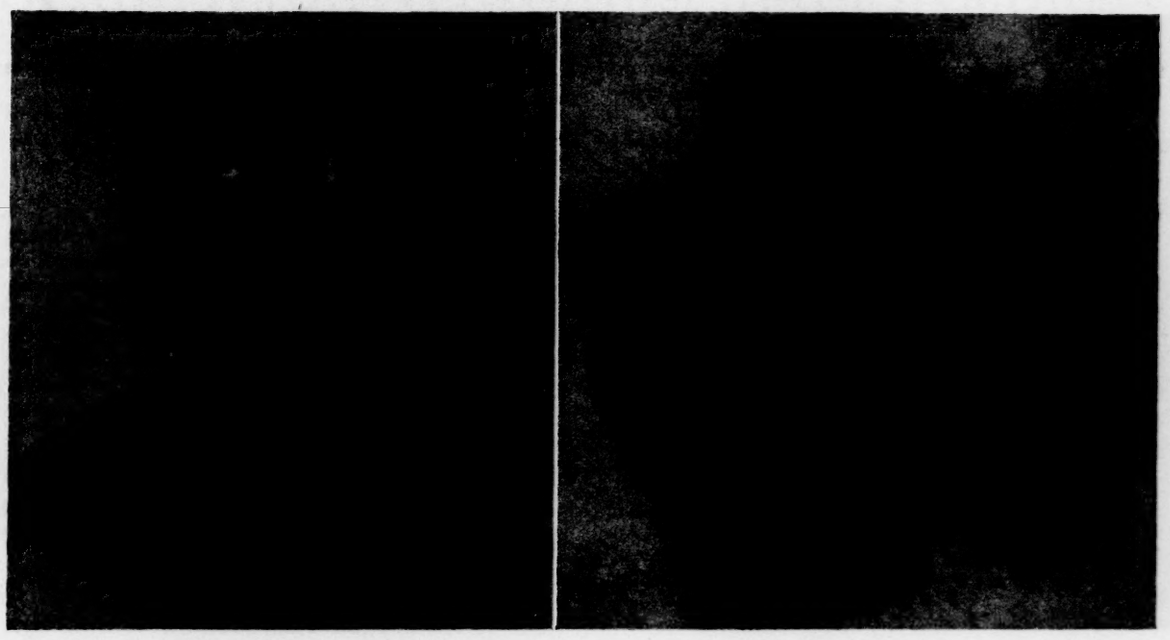
other clinical findings which have been noted are usually coincidental with the mitral stenosis and are frequently seen in cases of mitral stenosis alone (for example auricular fibrillation, congestive heart failure, cardiac murmurs, emboli). Furthermore, it has been pointed out that occasionally all of the classical symptoms of ball-valve thrombi may be found in cases showing only mitral stenosis.[10]

The similar effects produced by ball-valve thrombi and by large auricular clots explains the failure to differentiate these cases clinically. This explanation also accounts for the clinical similarity between cases of large left auricular thrombi and cases of left auricular tumor, as has been pointed out by Evans and Benson.[8] The postural effects considered to be characteristic of these cases may be due to the sudden increased requirement for blood resulting from increased exercise (e.g., sudden sitting up) or may be due to a cardiac output which is insufficient to supply the brain when the patient is sitting up but not when he is lying down, as in Stokes-Adams syndrome. It should be emphasized that the fundamental physiologic mechanism is that of diminished cardiac output and the resulting symptoms are the same regardless of whether the mechanism is due to a space-occupying lesion of the left auricle, severe mitral stenosis alone, severe aortic stenosis alone or Stokes-Adams syndrome.

It may well be that a ball-valve mechanism is a rather unusual occurrence and exceptionally difficult to prove. It would be necessary for the thrombus to be of a relatively small size in order not to fulfill the requirements of the mechanism described above. Furthermore, the presence of a loose thrombus of relatively small size in the left auricle is not conclusive proof that this is actually the explanation for the patient's symptoms. In one of our cases (Fig. 1) it is obvious that a thrombus must have remained lodged in the mitral orifice for a considerable period of time before death occurred. This conclusion is inevitable from the hour-glass appearance of the thrombus, yet the patient did not present the classical picture of a ball-valve thrombus.

Inspection of the accompanying photographs, as well as the gross and microscopic appearance of these hearts, indicates that these thrombi have been present for a considerable length of time and therefore probably are not responsible for the "sudden death" which has been emphasized so frequently in these cases. It is suggested that three possible mechanisms of death may be significant in these cases: (1) A diminished cardiac output with cardiac ischemia and sudden death which is analogous to the mechanism so frequently seen clinically and pathologically in cases of aortic valve disease and coronary sclerosis, in which death occurs before sufficient time has elapsed for the development of morphologic changes. (2) Further accretion of the thrombus in the left auricle exceeding a critical volume above which the amount of blood flowing through the left auricle and the mitral orifice is not compatible with life. (3) Regardless of its size, the thrombus may really be an incidental finding and the mechanism of death may be analogous to that occurring in patients who have only pure mitral stenosis with congestive heart failure. This last mechanism would be exceptionally difficult to rule out in any case except the occasional one in which death occurs in the absence of congestive heart failure or embolization, when life expectancy should be considerably greater.

The mechanism by which these thrombi form will be the subject of another presentation but certain explanations for the relative rarity of large left auricular thrombi are suggested. These include the following: Death of a patient



3 4

FIG. 3. Shows an adherent thrombus filling the left auricle with partial occlusion of the pulmonary veins (Case 3).

FIG. 4. Shows a thrombus 6 by 4 by 4 cm. in size which was found free in the left auricular cavity. A small clot was adherent to the wall of the left auricle and presumably represents the previous site of attachment of the free thrombus (Case 4).

due to other factors before sufficient time has elapsed for the development of a large thrombus; these factors include congestive heart failure and embolic phenomena. The second factor is a diminution in the size of the thrombus due to emboli which have dislodged from it and remained asymptomatic or unrecognized. This possibility is supported by the high incidence of old infarcts, not clinically recognized, in autopsy patients with rheumatic heart disease. The third factor is the organization and contraction of the mural thrombus with a resultant diminution in size. A fourth factor represents a largely unknown and most important mechanism, undoubtedly linked with blood coagulation and anticoagulant factors, which is responsible for the accretion of thrombi in any patient who presents intracardiac clots of antemortem origin.

CONCLUSIONS

1. Sixteen cases of ball-valve thrombi and large auricular thrombi have been studied and some of the relevant literature is reviewed.

2. An explanation for the clinical symptomatology produced by such occlusive auricular thrombi is presented and the responsible physiologic mechanisms are discussed.

3. The possible modes of death are described.

4. Various reasons for the relative rarity of this condition are suggested.

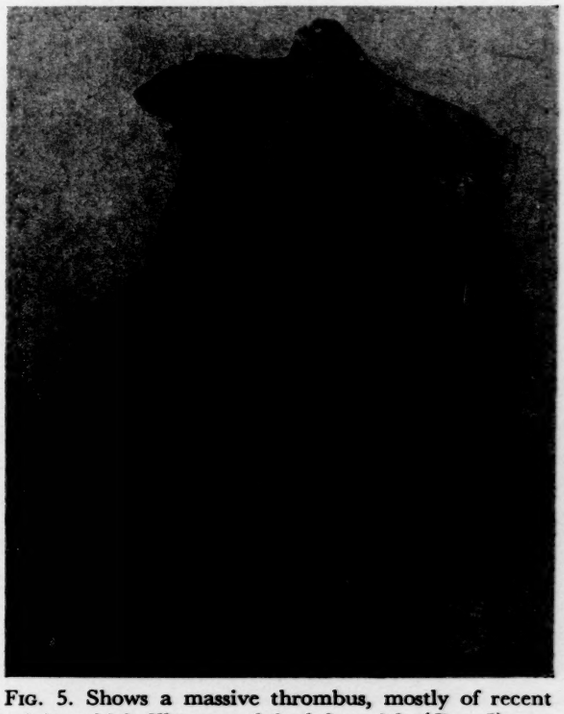


FIG. 5. Shows a massive thrombus, mostly of recent origin, which fills most of the left auricle (Case 5).

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Seminars on Neuromuscular Physiology

Muscle and Nerve—Physiologic Orientation*

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MOST organs of the body are concerned with the maintenance of dynamic equilibrium, including homeostasis; or with specific synthesis, including growth, reproduction and repair. In contradistinction, the nervous system and its attached receptors and effectors is concerned with the behavior of the organism in its environment, with adaptive amplification. The sensing, receiving, interpreting of experience—the input side of the story, in other words—is outside the scope of this article, although the problems and mechanisms involved in the evocation of a response in receptor elements by some environmental event, and the subsequent initiation of an impulse in the afferent nerve fiber, are entirely comparable and often identical with those seen on the motor side. In fact, the evolution of specific and great sensitivity of receptors to particular stimuli, which poured so much information into the nervous system that it sprouted a brain, in turn made possible, and occurred more or less in parallel with, a similar evolution on the motor side of the speed, specificity and power, which permit an appropriately differentiated, adaptive and selective behavior, or output.

The great job of the nervous system, in reworking input signals so as to give appropriate shifting patterns of activation of motor neurones, patterns both in space and in time, must also be omitted; although here again the mechanisms of synaptic transmission and those of metabolism and maintenance are surely close to those on the motor side. We must assume that the appropriate pathways and impulse volleys are playing upon the anterior horn cells as the fingers of the typist play upon the keys, so that the motor discharges start and stop in the various muscles of the body to produce the beautifully integrated movements that underly all behavior. Up to this "final common path," the nerve messages, potential fields, chemical mediators, or circulating substances are, in a sense, primarily contributing information to the system. From the motor horn cell on, information is limited to the simple binary of "yes" or "no"—the all or none law of nerve conduction assures this simple on or off character—and the problem is the much simpler one of the propagation of excitation or activation.

A nerve impulse has been defined as "a propagated tendency to excite," and our major problem now is to trace excitation out along motor nerves (noting interaction between them), across junctions (primarily the myoneural junction), into the muscle fiber and along the fiber membrane, and from the membrane to the contractile fibrils, somehow activated in the fiber interior. Conduction in continuous systems, such as cylindrical nerve or muscle, is a somewhat separate problem from transmission across discontinuities, as at the various junctions; but, in both, the questions of electrical and chemical mechanisms and of membrane or surface and interior aspects appear in comparable fashion.

Other aspects of the underlying physiology of nerve and muscle must receive more limited attention, although the role of resting metabolism in maintaining the integrity of the system and the related phenomena of degeneration, on the one hand, and the mechanisms and significances of the increased amount and, often, altered kind of metabolism associated with activity, on the other hand, are of major and general importance. Finally, only some of the special problems associated with particular structures and activities can be examined. Among these are: the very particular change in the membrane associated with activation; the regulation of reactions and energy release by mitochondria and the means by which this energy is effectively applied to other cell regions, especially the membrane; the mecha-

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nism of shortening by myofibrils, as well as the effective agent that activates them—all problems at the focus of interest of current research but which can receive only most inadequate consideration.

THE MOTOR UNIT

Coursing out through most of the cranial nerves and through the ventral roots are the slender extensions of the motor nerve cells. Running in a trunk with thousands of other nerve fibers, both afferent and efferent, the large (10–20 micra diameter) heavily myelinated, rapidly conducting motor fiber finds its proper way, suddenly branching within a few centimeters of its termination to innervate many skeletal muscle fibers. In a typical motor nerve about a half to a third of the fibers are myelinated (Sherrington, 1894), and some 60 per cent of these are the large motor nerves (Eccles and Sherrington, 1930; Rexed and Therman, 1948). The number of muscle fibers innervated by each motor nerve fiber varies from approximately one in certain muscles of the eye to about two hundred in muscles where power rather than fine control is needed (see Tiegs, 1953).

Under normal conditions this group of muscle fibers will contract as a unit (but see later) whenever the signal, relayed by the motor axon from the dorsal root afferents or descending paths from the higher centers, is given. The exact geometric distribution in the muscle of the fibers of any one motor unit is still uncertain (Tiegs, 1953), and it is not yet proven that the motor unit of the anatomist is identical with that of the electromyographer (Wohlfart, 1949; Denslow and Hassett, 1943). The pattern of innervation is not necessarily static, and intact nerves may "adopt" nearby denervated muscle fibers. Unfortunately, such reinnervation appears to be rather small in monkeys (Edds and Small, 1951) and thus presumably in man.

In any one nerve fiber each signal, each nerve impulse, is identical with its fellows, only decreasing in intensity if it should follow too closely upon the heels of the one ahead, and each motor unit has its private line to a particular central neuron. Normal skeletal muscle activity is graded in strength only by the participation of more or fewer motor units, and by the variation in the frequency of impulses in each motor nerve. The single nerve impulse resulting in a single twitch but rarely occurs outside the laboratory of the physiologist, a smooth tetanus being much more appropriate to the needs of the organism, and seldom is a muscle quiescent, or flaccid. Motor units are continually contracting in most muscles at rest, in some organized way, to hold the muscle in readiness for activity, to eliminate the need for the taking up of slack and to maintain posture against the pull of gravity. Likening this state to that of a tuned string, the Greeks called it τόνος (Cf. Sherrington, 1951, p. 201), and tonus it is today. There is, however, remarkably little electrical activity in the extensors of the back or legs in the relaxed, prone position (Denslow and Clough, 1941) or in the upright position when good balance is achieved (Floyd and Silver, 1951). Movement starts from posture and "posture follows movement like a shadow," but these are mainly problems of the central nervous system. Only one matter, of feed-back from the muscles, needs a word here.

Involved in the maintenance of tone, in the smoothing out of movements and in the follow-up of initial contractions with a steady maintained contraction, is an elaborate system of interconnected feed-back loops. Part of the integration involved occurs peripherally, in the muscle spindle, situated in the muscle mass in parallel with the large muscle fibers. On passive stretch, impulses from its annulospiral ending provide the afferent information for the two neuron stretch reflex. In addition, however, the small medullated fibers (from 3 to 8 micra diameter) provide efferent innervation to the spindle fiber (Kuffler, et al., 1951). Stimulation of these small motor nerves, although producing no detectable tension (in mammals), causes an active contraction of the spindle which puts its receptor element under more stretch, increases the frequency of afferent discharge and makes the receptor more sensitive to other changes in the muscle. In this way the "goal" at which the myotatic reflex shoots is altered and the tonus level at equilibrium shifted. Further, the small motor nerves are reflexly inhibited by impulses from the spindle afferents at the same time as these impulses reflexly excite the large motor fibers; so rough changes during a contraction tend to be smoothed out. These feed-back loops thus normally insure a well modulated rise and fall of tension. Still other ways in which the small motor nerves are involved in the regulation of reflex action, for example in the crossed extensor reflex (Hunt, 1952; Sherrington, 1909), are discussed in recent reviews (Hunt, 1952; Eccles, 1952).

In the frog, a similar group of small motor nerves innervates special muscle fibers instead of the muscle spindles (Hunt and Kuffler, 1950), and produces considerable tension and end plate potentials (see later) (Kuffler and Gerard, 1947; Hunt and Kuffler, 1950) but no propagated action potentials. These small fibers are here also involved in the maintenance of tone, but by a quite different and much simpler mechanism than in the mammal.

DEGENERATION

The nerve fiber, separated from its cell body, degenerates. This is not a kind of "atrophy of disuse" since maintained stimulation of the cut portion does not prevent the degeneration but actually accelerates it (Gerard, 1932). Presumably, then, a substance produced in the cell body is essential to the maintenance of the integrity of the axone. Since the latter has its own blood supply, bringing oxygen and substrate and carrying away waste products, the necessary substance would presumably be an enzyme and most likely a nucleoprotein from the cell nucleus. Much evidence exists for the movement of substances, including viruses, along nerve fibers and for changes in the rate of movement with activity and during regeneration; but a direct test of nucleoprotein movement with tracer phosphate proved negative (Samuels et al. 1951). On the other hand, a phosphoprotein compound was found to migrate peripherally at about 3 mm. a day, approximately the rate of growth of a regenerating axis cylinder. It has also been suggested that neurohumoral substances may migrate peripheralward in nerve fibers (Tainter, 1950), much as the posterior pituitary agents are now believed to migrate down from the hypothalamic nuclei in which they are formed (Scharrer and Scharrer, 1945; Bargmann and Scharrer, 1951).

The dependence of one element on another is not limited to the nerve fiber and its parent cell body, for muscle fibers also undergo dramatic degenerative changes when their motor fibers are cut. Relatively early in this process, the fibers exhibit continued fibrillation, thought by some to be due to a "hole" in the muscle membrane resulting from degeneration of the end plates, which serves as an electrical sink and from which propagated impulses continue to originate (Jarcho et al. 1953). It has also been argued that the muscle fibers degenerate as a result of excessive fatigue due to this fibrillation; but the fibrillation can be abolished by such agents as quinidine (Solandt and Magladery, 1940; Hunt and Kuffler, 1950), without preventing the ultimate degeneration of the muscle fibers. The excessive sensitivity of denervated structures to a variety of drugs has been widely demonstrated but not adequately explained (Cannon and Rosenbleuth, 1949).

Even more mysterious is the trans-synaptic degeneration seen, for example, when cortical neurons are destroyed and the thalamic nuclei with which they connect also disappear. This effect can hardly be attributed to a nutritional influence, or explained along the lines of the motor end plate degeneration in the case of muscle unless it be assumed that the pyramidal synaptic knobs are abnormally concentrated on the thalamic cell bodies. At least, deafferentation of spinal motor neurons does not lead to their degeneration, whereas stopping all afferent impulses to them does produce a state of lowered reflex responsiveness, which is overcome when impulses again flow (Eccles and McIntyre, 1951; Eccles, 1952).

Regenerating axones eventually find or recreate their proper peripheral connections, so that motor fibers reach muscle and the various afferent fibers reach their particular receptors. The mechanisms involved in this are not well known and are beyond our present scope (see Young, 1942; Weiss, 1950); but one practical point is the ability of a relatively small number of regenerating fibers to occupy the periphery, by excessive branching, so as to reinnervate a large number of muscle fibers. In effect, this enlarges the motor unit so that a single nerve fiber activates a disproportionately large group of muscle fibers. Attempts to improve motor power after disease losses, as in anterior poliomyelitis, by deliberately crushing a nerve trunk (neurotripsy) in the hope of obtaining a branching regeneration and so the activation of additional muscle fibers, have, however, met with little success (see Tiegs, 1953).

THE NERVE MACHINE

Excitation normally originates in a receptor, excited by an appropriate environmental state or change—and one of minimal magnitude suffices for the highly evolved organs—and the receptor activates an afferent nerve fiber. Central neurons can also be excited directly, as well as by sensory synapses, by chemical and other means; and there is increasing evidence that

some are true receptors in the more conventional sense. But our concern is with the discharge of the motor cell, activated directly or via a synapse and by electrical or chemical mechanisms, and the resulting nerve impulse destined to make some muscle fibers shorten.

Although the intimate nature of the nerve impulse is still the subject of intense study, perhaps no physiologic machine is so well understood as the nerve fiber and no action more rigorously analyzed. Since electric currents, carried by ions in protoplasm and tissue fluid, are so important in propagation, some attention to the ionic composition and electrical properties of nerve and muscle is required.

Architecture. The core of the nerve fiber, the axis cylinder, is a soft, rather transparent, jellylike substance apparently similar to the cytoplasm of other cells. The osmotic pressure is about the same as of blood, single axons act as almost perfect osmometers (Hill, 1950), and the electrical conductivity and diffusion rate of the principal cation, potassium, is only slightly less than in water solution, indicating its unbound state (Hodgkin and Keynes, 1953). The ionic composition of the axoplasm differs markedly from that of the body fluids (see Hodgkin, 1951), with the inorganic cations greatly exceeding the inorganic anions, and potassium present in large amounts as compared to sodium and chloride. Most data on axoplasm have been gathered on giant nerve fibers of marine invertebrates, in which the inorganic anion deficiency is made up by the amino acids aspartate and glutamate, and with alanine, taurine and glycine contributing to the high solute concentration necessary to balance the high osmotic pressure of the blood in these animals (Lewis, 1952). Much less is known of vertebrate nervous tissue. While the free amino acids have about the same relative distribution, except for a small aspartate content, in rat brain as in invertebrate nerves, the total amounts are small (Awapara et al. 1950); and their content in frog nerve is even smaller (Silber and Schmitt, 1940). The nature of the necessary water-soluble anions is still unknown.

The conducting core of the nerve fiber is surrounded by a relatively resistant membrane, up to thousands of ohms/cm.^{2} (the specific resistance, taking into account the thinness of the membrane, is actually about that of glass), with a high capacity (about 1 microfarad/cm.^{2}), and it is apparently in this membrane that the secret of the nerve's activity as a transmitter of information resides. It has long been known that the interior of the nerve is electrically negative to the exterior, but only in recent years have exact measurements of this potential become possible by the development of suitable microelectrodes, by the study of large fibers of invertebrates, and by the advance of instrumentation, particularly electronic stimulators, amplifiers, recorders, etc.

A small electrode was first inserted into a cell and the electrostatic potential measured with reference to an external electrode by Osterhout (1931) on plant cells. Today, microelectrodes are in widespread use for impaling all sorts of animal cells. It is possible to insert a capillary electrode of 50 micra diameter into the axoplasm of the giant axon of the squid, Loligo, often over half a millimeter in diameter, and to thread this electrode longitudinally in the fiber for a sufficient distance to avoid recording from the injured region of entry. When this was first done (Hodgkin and Huxley, 1939; Curtis and Cole, 1940, 1942), it was found that the membrane potential was not merely reduced to near zero during activity, as regularly supposed, but actually reversed in sign, the inside becoming positive with respect to the external medium. Most cells are too small to tolerate such an electrode, but Graham and Gerard (1946) succeeded in piercing muscle fibers with a capillary (ca 5 micra) small enough to produce little damage and adduced evidence that the membrane potential reversed in sign during activity in muscle as it did in nerve. Later improvements (Ling and Gerard, 1949) yielded a needle, less than 0.5 microns external diameter at the tip, which causes no detected damage on insertion and is now widely used to measure resting and active potentials. All excitable tissues so far studied have a membrane potential of about 80 mV and an action potential half again as large as this resting potential (see Huxley and Stämpfli, 1951). An ingenious method of measuring the absolute resting and action potential of single myelinated fibers with external electrodes (Huxley and Stämpfli, 1951) has yielded like results.

Metabolism. The electrical changes that occur in the nerve fiber when it is signalling the muscles to contract are negligible in terms of energy. But the nerve impulse does not coast and energy for propagation, as well as for simple maintenance, is provided by the meta-

bolic mechanisms, which recharge the machinery for succeeding impulses. Like any other cells, nerves depend ultimately upon metabolism to maintain their integrity and to function. Conduction fails in the absence of oxygen (Fillie, 1908); the resting membrane potential falls when respiration is prevented (Gerard, 1930) and even more rapidly when glycolysis also is inhibited (Ronzoni, 1931; Chang and Gerard, 1933; Shanes and Brown, 1942); and activity is normally accompanied by an increased oxygen uptake and heat production (see Gerard, 1932; Feng, 1936). What fuels are oxidized is still in question (see Gerard, 1946); but the increased oxidations of activity are not supported by carbohydrate although this is used at rest and by brain. Nerves may conduct a million impulses without extra oxygen consumption, however, as in the presence of azide (Doty and Gerard, 1950; Brink et al., 1952) or of chloretone (Bronk and Brink, 1951), so that this energy is not immediately necessary. As will be seen, nerves gain sodium on activity and must later pump it out with the expenditure of considerable energy; perhaps those conducting without extra oxygen consumption continually gain sodium, as discussed by Brink et al. (1952).

A wealth of detailed information is available concerning chemical changes which occur in intact or extracted tissues, but little is known about how these are linked with function. Use of sensitive and rapid methods, such as the oxygen cathode (Connelly and Bronk, 1948; Carlson et al., 1950), has permitted quantitative description of the relation between oxygen uptake and frequency and duration of trains of impulses (Brink et al., 1952). Such evidence indicates an important role of oxidative phosphorylation in conduction (Abood et al., 1952; Brink et al., 1952), and it is relevant that this chemical coupling is inhibited by azide in the same dose that inhibits the oxygen consumption of activity but not of rest (Mullins, 1950; Fries et al., 1942).

Recent evidence indicates that oxidations occur in the mitochondria (in which azide also decouples phosphorylation; Loomis and Lipman, 1949) and the question is thus acute—how do processes occurring in the membrane alter processes occurring in the mitochondria and, conversely, how does energy released in the mitochondria serve the needs of the membrane? In medullated nerve, at least, the mitochondria are heavily concentrated at the nodes of Ranvier (Gasser, 1952), where energy is probably most needed; and the increase of inorganic phosphate and its acceptors by breakdown of the energy-rich esters (ATP and CrP) leads both to increased oxygen consumption (Abood and Gerard, 1953) and oxidative phosphorylation (Potter and Recknagel, 1951). ATP may be involved in ion exchange by mitochondria (Davies and Krebs, 1952) and electric stimuli can induce in brain slices (McIlwain et al., 1951) or mitochondria suspensions (Abood et al., 1952; Abood and Gerard, 1953) the metabolic changes seen in active brain. It is significant, though, that the fall of phosphate esters which accompanies increased oxidation, is not due to their more rapid breakdown but to inhibition of their formation.

Eddy Currents. Regardless of the specific mechanisms involved, the property of the nerve impulse which insures its propagation from one node of Ranvier to the next, or to contiguous regions of an "unmyelinated" nerve, resides in the currents which flow as a result of the membrane potential change of the active region.

The picture of nerve conduction—of a polarized membrane of high resistance "punctured" as its polarization is decreased, the resulting active region becoming a sink for currents from a neighboring nerve region, which in turn becomes depolarized and active—was a hypothesis a few decades ago but is today an experimental fact. The potential across the membrane has been measured between an external electrode and a micro one impaling the single nerve or muscle fiber (Ling and Gerard, 1949; Hodgkin, 1951), the initiation of the active response at a critical level of depolarization has been similarly measured (Jenerick and Gerard, 1953), the increase in ion permeability, especially to sodium, that occurs at this time has been proven by electrical measurements (Hodgkin, 1952; see Ussing, 1952; Larrabee and Edwards, 1953) and by tracer chemical technics, and the existence and importance of eddy currents between active and inactive regions has been established in many ways.

For example, although a nerve impulse be blocked by a cold band, the eddy currents swirl on ahead and partly activate the distal portion of the nerve, as shown by a considerable decrease in threshold beyond the block at the appropriate time (Hodgkin, 1937 *a,b*). Even more clearly, when a millimeter or so of a single nerve fiber

is blocked by a droplet of a narcotic solution the impulse will jump this inert stretch if the regions above and below are connected by a good external conductor (Tasaki, 1952). Along these same lines, the impulse travels more rapidly in a given fiber when the external resistance is lowered, as by increasing the amount (Hodgkin, 1939) or the conductivity (Pond, 1921) of the bathing solution, or when the internal resistance is low in a large diameter fiber as compared to a small one (Rushton, 1951; Hodes, 1953). In each of these cases a given action potential serving as a battery causes more current to flow a greater distance and so produces the needed depolarization sooner or further along the resting fiber. In fact, the velocity of conduction in a variety of fibers can be precisely expressed in terms of the size of the action spike, the threshold of the resting membrane and the electrical constants of the circuit (Rashevsky, 1948).

The only paragraph of the entire story which is not written today involves the actual nature of the membrane change produced by depolarization. The earliest effect of applied currents, whether an external stimulus or eddys from an already active region, is a physical discharge of the condensor-like membrane. But soon an active process of some sort is added to the passive one and the fiber develops a prepotential—a greater and more prolonged depolarization (see Katz, 1939; Eccles, 1946). When this prepotential is sufficiently great—that is, when the membrane potential has been reduced to the critical level, a fall of about one-third of its initial value—a further explosive change in properties occurs and the propagated impulse is irrevocably discharged. A local potential below the critical level fades out without an impulse propagating; on reaching the critical level, the potential change becomes abrupt, continues until the charge is reversed from the initial outside positive to outside negative (the action spike), and the membrane resistance falls from thousands to tens of ohms per square centimeter (see also Katz, 1952).

The eddy currents not only activate other parts of the fiber that generates them but also, through their external loops, act upon adjacent fibers. As an impulse in fiber A passes a given point in fiber B, these eddy currents will first flow into B while the sink in A is still approaching, will flow out of B as the active sink is abreast the point, and will then flow into B again when the sink has passed. Such anodal, cathodal, anodal polarization should make the threshold of B first higher, then lower, and eventually higher again; and experiment demonstrates exactly this (Marrazzi and Lorente de Nó, 1944).

Clearly, if fiber B were unduly sensitive or the currents from fiber A unusually large, or if the anatomy were such that the second wave of anodal polarization were eliminated, as does occur at a region of branching, the impulse in fiber A might actually excite fiber B. This would constitute a case of transmission across a junction, and such an artificial synapse (often called an ephapse) has been deliberately produced or demonstrated to occur under a number of conditions. When fibers have been rendered excessively irritable—by lowering the external calcium, by cathodal polarization, by a cut nearby, which also depolarizes—impulses cross from one fiber to another (Arvanitaki, 1942; Jasper and Monnier, 1938; Granit et al., 1944). This mechanism has been suggested as the basis of causalgic pain (Doupe et al., 1944), currents from motor fibers being assumed to spread into and excite adjacent non-medullated sympathetic fibers in an injured region of the nerve trunk. It is doubtful if such ephatic action occurs here (Gerard, 1951), but it certainly can occur *in vivo* at damaged peripheral nerves or central tracts so as to produce pseudo reflexes from the region of damage. Indeed, such ephapses exhibit many of the properties of true synapses and normal reflexes, including irreciprocal conduction, presynaptic summation, synaptic delay, and multiple post-synaptic discharges from single presynaptic impulses (Granit et al., 1944). In these cases, the mechanism of transmission from one element to another is unequivocally, by means of the electrical currents, flowing; which strongly suggests the existence of a similar mechanism in transmission across normal junctional regions.

Conduction in unmyelinated nerve and in muscle is a uniform process, while in the myelinated nerve the excitation jumps from node to node, the transmission is discontinuous or saltatory (Tasaki, 1952; Frankenhaeuser, 1952). As suggested] by Lillie (1925), the swirling eddy currents find no return path through the highly resistant myelin sheath and are forced to flow through the membrane of the neighboring nodes. In Lillie's model no current whatever flows through the myelin, excitation leaps ahead and conduction rate is

determined by the delay in the excitation process at the nodes. On this theory conduction velocity should be proportional to the distance between nodes for nerves of equal diameter. In fact, considerable capacity current flows through the myelin (Hodler, Stämpfli and Tasaki, 1952) and the main factor in many cases which determines the conduction velocity is the delay caused by the passive spread of potential along the inert internodal myelin "cable." On this basis, the propagation of the active response is truly saltatory while the external recorded action potential may not appear to be so, and the simple relation between conduction velocity and internode length would no longer be expected.

The Membrane. Sherrington (1951, p. 198) was fond of referring to nerve impulses as "transient self-mending electrical leaks travelling along nerve-fibers." That a change in the ion permeability of the membrane might be basic to the electrical change during activity was suggested in the theories of Bernstein (1912) and Lillie (1923). The Bernstein hypothesis regarded the resting membrane as selectively permeable only to the potassium ion, which was prevented from flowing out, despite its high inside concentration, by the electrostatic attraction of the anions held inside. This should produce a potential across the membrane of the correct sign and approximately correct magnitude. On this theory, the sodium ion remained outside because of its inability to penetrate. On activity, the membrane was supposed to "break down" and permit all ions to pass freely, dropping the potential to zero.

This was a satisfactory theory for decades, but difficulties appeared when Fenn showed that sodium could exchange for potassium (1936) and, from osmotic experiments on muscle, Boyle and Conway (1941) had to conclude that this membrane is permeable to chloride as well. More recently, exchange of all these ions has been demonstrated for nerve and muscle by the use of isotopes, and many detailed studies made (see Ussing, 1949; Krogh, 1946). Finally the observation that the membrane potential reversed during activity was fatal to this theory in its original form. Boyle and Conway (1941) could account for the resting potential and other facts, but not for the active reversal of membrane potential, by regarding the membrane as permeable to potassium and chloride but not to sodium or to other internal anions. The reversal has been satisfactorily explained by Hodgkin and Katz (1949; and see Hodgkin, 1951; 1952; Eccles, 1952), in collaboration with Huxley, by assuming that during activity the resting conditions are reversed so that the membrane becomes relatively more permeable to sodium than to the other ions. Since the internal sodium concentration is small compared to the external one, the reversed sodium-potassium permeabilities should result in a reversed potential as sodium enters the fiber at a high rate. The sodium would also provide the current to depolarize and excite adjacent regions of the nerve (or muscle).

Following the drop in the membrane potential with sodium entry, which allows some potassium to flow outward, there is a second increase in permeability, this time favoring potassium which accelerates the potassium loss. The outgoing potassium balances the incoming sodium and restores the membrane potential to normal before the increased sodium permeability has fallen back to its resting value. The immediate source of energy for conduction is thus provided by the sodium and potassium interchange, the osmotic engine running down a bit, and metabolic energy must ultimately restore the potassium lost and "pump out" the sodium gained. The amounts exchanged, however, are so tiny that millions of impulses could be transmitted before the concentrations of these ions would be significantly altered. In any event, sodium does enter during activity and must be pumped out against both an electrical and a concentration gradient to maintain a steady state. Other instances, including red corpuscles, frog skin and kidney cells, in which sodium is pumped against an electrochemical gradient, are discussed by Ussing (1949).

Just as the active response of nerve can be initiated by many agents—electrical, chemical, thermal, mechanical—so the response can be blocked in many ways. As mentioned earlier, changes in action spike height, related to membrane potential, and in excitation threshold, also related to membrane potential, will alter conduction. Normally, a factor of safety of about five (Gerard, 1932; Tasaki et al., 1941) ensures propagation; but when spike fall or threshold rise, or both, exceeds this five-fold leeway, block results. Blocking agents can be grouped into depolarizers and non-depolarizers (Bishop,

1932), the former mostly reversible on repolarizing the membrane by applied anodal currents (Lorente de Nó, 1947). The non-depolarizers are usually associated with increased threshold—low sodium, procaine, methyl fluoracetate, etc. (see Boyarsky et al., 1949; Butler, 1950; Toman, 1952).

THE MYONEURAL JUNCTION

As the nerve impulse approaches the muscle fiber a critical region is encountered. The local currents which flow ahead of the active region must effect the propagation, but this is made more difficult when the single axone branches into many twigs of much reduced diameter and with a vastly increased surface to volume ratio. Moreover, just before the nerve penetrates the sarcolemma it loses its myelin sheath, to terminate in a complex ending—which varies widely from species to species (Tiegs, 1953)—a vulnerable region where trouble is inevitable.

The transmission of excitation from nerve to muscle has been studied in many peripheral junctions. Histology has been of singularly little help here, and most knowledge has come from pharmacologic and electrophysiologic studies. Since acetylcholine is a transmitter at parasympathetic endings and noradrenalin at orthosympathetic ones, the kind of transmitter, or even the existence of one, at motor nerve endings was long problematical. It was shown in 1936 (Dale, Feldberg and Vogt) that stimulation of the motor nerves resulted in liberation of small quantities of acetylcholine (ACh) from muscle, and shortly thereafter that close intra-arterial injection of ACh produced a contraction (Brown, Dale and Feldberg, 1937). With the discovery of the end-plate-potential (e.p.p.) (Göpfert and Schaefer, 1938) a lively debate began between proponents of the "electrical" and the "chemical" theories of neuromuscular transmission. Since the fundamental mechanisms for either type of transmission seemed to be present, the question could be answered only by exact quantitative knowledge. This is now becoming available by the use of the intracellular electrode on single junctions (Fatt and Katz, 1951; Nastuk, 1953; see Eccles, 1952).

The e.p.p. is a response of a specialized region of the muscle fiber membrane and not of a separate "end-plate" membrane or of the nerve membrane; and it is significant that when an "antidromic" muscle impulse and a nerve impulse arrive together at the junction, the e.p.p. is blotted out at the time but its residue still builds up subsequently (Kuffler, 1942). Moreover, electrical stimulation of the end-plate by an impaling electrode seems to be impossible (Fatt and Katz, 1951), and the amount of charge which passes across its membrane during one impulse—3×10^{-9} coulombs or 3×10^{-14} univalent ions for the normal frog sartorius, one-fourth this under curare and fifteen times as much under prostigmin—is of the order of the total ionic content of the terminal nerve twig. With an electrically controlled pipette, Nastuk (1953) succeeded in stimulating the motor end plate (but no other region of the muscle membrane) by external application of a very small amount of ACh, estimated to be as little as 5.5×10^{-15} equivalents; but (unpublished) injection of even larger quantities was ineffective. The evidence for a transmitting agent is thus strong at present and ACh is a likely candidate.

One picture of the sequence of events has been presented by Fatt and Katz: When the nerve impulse reaches the termination, a minute quantity of ACh is released, diffuses to the adjacent, specially sensitive area of the muscle membrane, and combines there momentarily with receptors. This leads to an increase in permeability to all ions (of the type postulated by Bernstein), a consequent fall of the membrane potential to a low value, the flow of eddy currents into this sink from neighboring regions, and the usual initiation and travel of an all-or-none impulse in the muscle membrane. The ACh is then split by the cholinesterase, now shown by cytochemical methods to be strikingly localized at the junction (Koelle, 1950, 1951; Couteaux, 1951). In this scheme drugs could act by changing the amount of ACh released per impulse, the rate of its destruction, the sensitivity to it of the specialized end-plate region, or the response of the muscle membrane away from the end-plate to the e.p.p. With so many parameters, many confusing phenomena can be reconciled.

The calcium ion, for example, appears to act in two ways. Decreased calcium results in decreased release of ACh from the nerve endings, at least as indicated by a diminished e.p.p., without change in the sensitivity of the end plate to applied ACh (Castillo and Start, 1952; Fatt and Katz, 1952); but before block results the motor nerve fiber is set into repetitive activity. This produces a spontaneous twitching

which can be stopped by curare; but ultimately the lowered threshold of the muscle membrane results in spontaneous activity of the muscle itself. Conversely, Ca increase augments the e.p.p., presumably due to increased ACh output, yet ultimately blocks by raising the threshold of the muscle membrane until the e.p.p. is ineffective.

As a second example, anti-cholinesterases, such as eserine or DFP, cause an increase in twitch height to a single stimulus, due to repetitive firing of the muscle, an increased depression of response to high frequency nerve stimulation, and an altered response to injected ACh. At low concentrations the e.p.p. is considerably prolonged, while at higher concentrations its amplitude is markedly decreased. These effects cannot readily be explained if the antiesterases only inhibit the breakdown of ACh. If, however, they can compete with ACh for sites on the esterase, they might also do so for sites on the postulated ACh receptor in the end-plate. Then, the low concentration of eserine would prolong the e.p.p. by virtue of its antiesterase action while the high concentration would lower the e.p.p. by its action on the receptor sites. Curare appears to act at this same point, its inhibition of ACh contracture of the frog's rectus abdominus being the result of competition (following the Michaelis-Menten equation) for a common receptor (Kirschner and Stone, 1951).

While the evidence for the involvement of ACh in neuromuscular transmission is now good, a role in nerve and muscle conduction remains most improbable (Gerard, 1946; 1950; compare Nachmansohn 1952). Eserine or DFP can block nerve, but without initial prolongation of the action potential and only at concentrations far above those needed to inactivate ChE. ACh, outside or injected into a muscle fiber, has negligible effect on the membrane potential (Gerard, 1946) and is also inactive inside the end plate region (Nastuk, 1953); while curare injected into the squid giant axon produces block in minute quantities (10^{-11} gm d-tubocurarine chloride), some ten thousand times less than the amount of anti-cholinesterase required to block (Grundfest et al., 1952).

MUSCLE

An action potential, set up in the muscle membrane by eddy currents starting normally at the end plate, propagates just as in nerve, but more slowly relative to diameter and with a relatively large and enduring negative after potential (Nastuk and Hodgkin, 1950; Taylor, 1953). Modern technics permit precise recording of muscle action potentials in man and electromyography is widely used to measure functional impairment, resulting from central nervous system lesions, peripheral nerve injury and neuromuscular junction disorders (see Hodes, 1953; Tiegs, 1953). Recent work indicates that not all the muscle fibers in a motor unit need contract with each impulse; they do so only if a certain amount of facilitation at the neuromuscular junction is present, as produced by stretch (Libet and Feinstein, 1951) or repetitive stimulation. Such studies have been carried out on intact but "isolated" human muscles in amputees with cineplastic muscle tunnels by the California Biomechanics Research Group (see Hodes, 1953).

Activation of the Contractile Elements. The conducted activity in the muscle membrane somehow results in the initiation of contraction in the fiber. It is highly unlikely that the local eddy currents which flow during activity are involved here (Kuffler, 1946; Sandow, 1950; Taylor, 1953). A local contracture (a prolonged, reversible, non-propagated shortening, as defined by Gasser, 1930; not the clinical meaning of any prolonged contraction, including structural shortening and tetani) is produced where a sufficiently strong current flows out through the fiber membrane, even when the action potential mechanism has been blocked, as by procaine. In a fresh muscle, however, the threshold for such a contracture is greater than that for the propagated response (although the reverse is true with high K^+ and low membrane potential; Jenerick and Gerard, 1953); so that the membrane current, spreading ahead of the action potential but reversing direction as soon as the new membrane region is excited, can never reach the threshold value for shortening.

Contracture, although accompanying cathodal currents, directed outward through the membrane, does not accompany inward membrane currents nor those directed longitudinally along the fiber. Moreover, contractures can be induced in many ways without membrane depolarization; most striking, perhaps, being the post-anodal contracture which appears at normal membrane potential after a prolonged inwardly directed current is stopped (Taylor, 1953). So it is unlikely that membrane de-

polarization as such, whether accompanying a propagated spike or otherwise induced, is the effective stimulus to shortening.

The individual fibrils are the contractile elements of a muscle fiber (see below) and some can be made to shorten without others in a given fiber (Barer, 1948). Yet, as a wave of contraction passes down the fiber, the cross striations remain in perfect alignment (Hürthle, 1909), indicating that those in the interior or near the surface shorten in precise unison. This, plus the speed of activation (Hill, 1951, and below), argues against activation depending on the simple diffusion of a substance from the membrane toward the center. Some aspect of the conducted activity, then, but neither the potential or the local currents *per se*, initiates a process which moves inward from the membrane of the fiber, too rapidly to be simple diffusion, and leads to shortening of the fibrils.

Shortening does not begin for about 3 msec. (frog sartorius, 20°c.; Nastuk and Hodgkin, 1950) after the local region is effectively stimulated. There are, however, signs of activity during this period which may lead to understanding of the activation mechanisms. Earliest in the latent period the muscle elongates slightly, the so-called "latency relaxation" (Rauh, 1922; Schaefer and Göpfert, 1937; Sandow, 1944), and changes its light diffraction (Hill, 1949, 1953; compare nerve, Hill, 1950; Tobias, 1952). Other physical changes associated with activation or contraction involve pH, volume constriction, other optical properties and impedance; but some are not invariably associated with the onset of tension (see Mommaerts, 1952). Electric changes, other than the action potential, are absent (Taylor 1951, 1953); heat will be discussed shortly. Also during the latency, extensibility of the muscle is sharply decreased (Gasser and Hill, 1924).

Whether the delay in shortening documents a period of activation (see Mommaerts, 1950) or results from a mechanical lag in the system (Brown 1941; Hill, 1950) is still moot. But the finding (Hill, 1953) that, following a slight release of a muscle during a maintained isometric contraction (only 3 per cent of the muscle length), the tension drops to zero but rapidly redevelops along a curve of tension versus time like that at the beginning of a tetanus, is difficult to reconcile with the view that the delay in initial development of tension is due to a gradual activation of the contractile machinery. The rapidity of events during the initiation of contraction probably precludes their identification by traditional chemical methods, while physical methods are rarely specific, spectra being perhaps the main exception, with regard to chemical identification.

The Mechanism of Shortening. While propagation in the membrane of nerve or muscle is "all-or-none," the contractile response of the muscle is not. The twitch is normally all-or-none because the propagated stimulus is so; but since the twitch long outlasts the action potential, and a second stimulus can be propagated before the mechanical events have reversed themselves, mechanical responses can sum and produce a greater contraction with repeated stimulation. Stimuli repeated sufficiently rapidly produce, besides a greater contraction, a smoothly maintained shortening or tension; but even then some processes (optical diffraction; Nicolai, 1936) follow the tetanization frequency at least to 200/sec.

In the same year (1847) that he communicated his celebrated work on the conservation of energy, Hermann von Helmholtz submitted a paper on the measurement of heat production of muscle (see Fulton, 1926). Due largely to the work of A. V. Hill, this subject is well developed and has led to important conclusions regarding contraction. The resting muscle, in common with "elastic" tissue, has a "rubber-like" elasticity, and shortens when warmed (Meyer, 1952). This is in contrast to the "normal" elasticity of contracted muscle and of connective tissue and tendon, which lengthen when warmed. Since rubber-like elasticity has been satisfactorily interpreted (Treloar, 1949), much work on muscle (Hill, 1952) and on specially treated muscle fibers or actomyosin threads (Szent-Gyorgyi, 1951; Botts, 1951; Botts et al., 1951; Morales and Botts, 1952) has been based upon it, but the problems involved are by no means solved. One difficulty is that the thermal changes produced in resting muscle by stretch or release are not simultaneous with the tension changes, and it is questionable whether a true equilibrium to which thermodynamic principles may be applied is ever present (Hill, 1952).

Activity of muscle is associated with two main phases of heat production, initial and delayed, in addition to the resting heat production. The delayed heat, about half of the total, seems to be related largely to restitution pro-

cesses, lasts for minutes following activity, and is closely associated with the increased oxygen consumption of activity (D. K. Hill, 1940). In absence of oxygen, the delayed heat is reduced to about one-twelfth its aerobic value; and with glycolysis also inhibited by iodoacetic acid, it is abolished. The initial heat is insensitive to the presence or absence of oxygen. (In nerve, by contrast, the delayed heat constitutes up to 97 per cent of the total heat and is no more sensitive to anoxia than is the initial heat.)

The initial heat consists of a maintenance heat, continuing at a given *rate* as long as the contracted state lasts and a shortening heat, an added *amount* depending upon the extent of shortening but independent of the particular work done (the Fenn effect). No true relaxation heat occurs (Hill, 1949), any heat at this time being the result of work done on the muscle by an external load. Such facts lead to important conclusions: (1) The energy released by a contracting muscle is determined by, and adapted to, the needs of the moment; it is determined during, not prior to, the contraction; and (2) the processes involved in the active state are, on balance, exothermic, and there is no further heat release on relaxing from this state. These present difficulties to any "post-energization" type of theory, in which contraction is the thermodynamically spontaneous phase of the cycle (e.g., Pauling and Corey, 1951). Recent work on extracted fibers, to be discussed shortly, is illuminating here (Weber, 1952). Skeletal muscle contains about 20 per cent of protein, of various sorts (see Mommaerts, 1950). Of these, a special fraction, the myosins, appears to be directly associated with the contractile mechanism. First extracted and studied by Kühne (1868), they have received intense study in the past decade or two (see Weber, Edsall and von Muralt, 1947; Szent-Gyorgyi, 1951; Mommaerts, 1950), and their ability to change length under the influence of ATP and other inorganic ions is established. While the energy for contraction seems to derive from the dephosphorylation of ATP, the mechanisms are not yet clear.

Fiber models of the complex, actomyosin, formed as extruded threads of oriented protein molecules, have been made to change shape under many conditions, not always close to those operating on the contractile system in muscle; but models of single muscle fibers, extracted with water and glycerol (Szent Gyorgyi, 1951), or of muscle strips, put into rigor with IAA, frozen, and then thawed in 0.04M KCl and 0.004M $CaCl_2$ (Perry, 1950), have many properties strikingly similar to those of intact muscle (see Weber, 1952). These models, like muscle, contract on addition of ATP and catalyze its hydrolysis; they develop the same tension and it has the same dependence on temperature (the large maximal shortening, about 80 per cent, is more like smooth than skeletal muscle); they pass into rigor at a low concentration of ATP and increase their resistance to stretch; they lose tension on quick release and regain it characteristically; and they show, on contraction, the typical decrease in birefringence and exhibit distinctive axial and transverse x-ray patterns (Huxley, 1953).

These appear, therefore, to be good models, uncomplicated by metabolic phenomena, and study of them has led to the following conclusions (Weber, 1952): They contract on the addition of ATP (or inosinetriphosphate) only when it can be split; the contractile system receives energy only during the contraction phase, relaxation being the thermodynamically spontaneous process; relaxation occurs with low ATP in the presence of polyphosphates, when the catalytic splitting is prevented, and on addition of a newly discovered factor (a non-dialyzable protein and a large, heat-labile dialyzable component of molecular weight about 10,000) normally present in muscle (Marsh, 1951; Bendall, 1952).

In the absence of polyphosphates and of this protein factor, washing out ATP produces in these models a condition closely resembling rigor mortis. In intact muscle, also, rigor ensues when ATP is gone (Ling and Gerard, 1949) and in brain a variety of observations (Abood et al., 1952; and unpublished) suggests that overactivity may be a consequence rather than (or as well as) a cause of lowered energy-rich phosphate. Certainly, in many instances of response, synthesis of ATP is decreased rather than its splitting increased and turnover rate is slower rather than faster. Moreover, ATP injected into a muscle fiber is inactive, while externally applied ATP evokes repeated normal twitches (Falk, 1953; and unpublished). Other current research (Taylor and Abood, 1952) shows that the CrP content of muscle can be raised or lowered by subthreshold currents crossing the membrane; again suggesting a role of these energy-rich phosphate esters in relation to the activation process rather than the contractile

response. But such heresies demand further research to test their worth.

The structure of the skeletal muscle fiber is complex, and the exact distribution and state of the proteins in it is not known; nor has any theory of the significance of the crossbanded appearance gained wide acceptance. The muscle fiber is a bundle of myofibrils embedded in a matrix of sarcoplasm, and surrounded by a remarkably delicate sarcolemma. The myofibrils are not artifacts of observation; they are the fundamental contractile elements of the fiber. Early optical studies of the many cross bands—A, I, Z, M, N, H—have been confirmed with the electron microscope (Hall et al., 1946), but the protein chains appear to pass continuously through the bands and the evidence is against the existence of transverse membranes. What keeps the separate fibrils so accurately aligned that bands cross the whole fiber as sharp lines, and any utility of this, remains unknown.

The sarcoplasm is a little-studied viscous gel containing protein, mitochondria, fat droplets and glycogen and is probably the site of the metabolic activity. Whether it also is contractile generally, as it is in certain cells, is not settled; but, of course, contractility is not limited to "muscle" cells, nor indeed even to systems with visible fibrillae—amebae move, and cilia wave (cf. Fenn, 1945)—and the particular structure of the skeletal muscle fiber is undoubtedly related to the great power and speed of the response rather than to the existence of contractility.

Surrounding each muscle fiber is the sarcolemma, a thin membrane described and named by Bowman (1840), and outside this is a separately visible adventitious connective tissue membrane, frequently miscalled the sarcolemma. The inner membrane, about 0.1 micron thick, and so at the limit of resolution of the light microscope, is probably not collagenous (Barrer, 1948) and may well be the "plasma membrane" involved in the ionic interchanges and electrical potentials (see Tiegs, 1953; Pease and Baker, 1949).

Much of our knowledge of cell metabolism has been obtained from the study of extracts of muscle, and most facts are still to be interpreted in terms of processes occurring in the intact cell. Study of muscle gave the first definite indications of how metabolism might be linked to function, via energy stored in the high-energy phosphate bonds of ATP and transferred appropriately from it. A main function of metabolism, both aerobic and anaerobic, is apparently to maintain and replenish this store of ATP (see Mommaerts, 1950).

Since man began to wonder, this curiosity about nerve and muscle has repeatedly led him into undreamed paths of investigation. The early development of mechanics, the concept of force, the storage battery, the string galvanometer, the thermocouple, the principle of the conservation of energy, the protein; these and more owe their existence in large part, or wholly, to the study of nerve and muscle. It is only proper that it should be so; for a man *does* nothing, communicates nothing, except he contract a muscle by way of its motor nerve.

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Combined Staff Clinic

Bone and Metabolic Diseases of Bone

THESE are stenotyped reports of Combined Staff Clinics of the College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital, New York. The clinics, designed to integrate basic mechanisms of disease with problems of diagnosis and treatment, are conducted under the auspices of the Department of Medicine. The reports are edited by Dr. Gilbert H. Mudge.

DR. CALVIN H. PLIMPTON: In undertaking this Combined Staff Clinic on so obscure and controversial a subject as bone and metabolic diseases of bone, we appear before you as a group of humble pilgrims, plodding hopefully forward in a manner reminiscent of John Bunyan's hero, Christian, as he floundered through Pilgrim's Progress. Dear friends, perhaps you will join us on this pilgrimage, for I can see among you several of Christian's friends—Mr. Worldly-wiseman, Mr. Facing-bothways, Mr. Valiant-for-truth, Masters Ready-to-halt, Sleepy-head and Greatheart. There are even Mrs. Light-mind and Miss Know-nothing.

We will start where Christian managed to get out of the Slough of Despond. He started to make a slight detour over to a Mount. This was an unusual Mount in that pieces of it were apt to break off and smash pilgrims to death. Of course, you will remember that this was called Mount Sinai. But rather than subject you to the danger of being smashed by taking you to the mountain, I have brought the mountain to you. It is a great pleasure to introduce Dr. Alexander B. Gutman, Director of Medicine at The Mount Sinai Hospital, and let him lead us away from the Slough of Despond and tell us something about the nature of bone.

DR. ALEXANDER B. GUTMAN: We are apt not to appreciate the importance, the beauty and the extraordinary complexity of the structural framework of the body, the skeleton; a system which constitutes 15 to 20 per cent, wet weight, of the total body weight. It is more than an inert rack upon which the soft tissues of the body are suspended. It is a most ingeniously contrived mechanism, cunningly put together to provide at once, without undue burden of weight, both essential rigid support for the organs and flexibility for movement. The skeleton is, moreover, the repository of some 99 per cent of the total calcium and some 90 per cent of the total phosphorus stores of the body, and is, in addition, an important depot of sodium, carbonate and other essential electrolytes. As such it serves a significant function in maintaining the *metabolic* as well as the *structural* stability of the body.

The bone is not a primitive but a highly specialized tissue. The rigidity and strength with which it is endowed are provided by impregnation of the osteoid matrix, a complex composed largely of proteins (chiefly collagen) and mucopolysaccharides (chiefly chondroitin sulfates) with a mineral, the bone salt. This bone salt is deposited in the matrix in the form of myriads of tiny microcrystals of well defined lattice structure.

The lattice of the bone salt crystal, as revealed by x-ray diffraction patterns, has the structure of an apatite. But whether the bone salt is, more precisely, an hydroxyapatite, $Ca(OH)_2 \cdot [Ca_3(PO_4)_2]_3$, or alpha tricalcium phosphate, $H_2(OH)_2 \cdot [Ca_3(PO_4)_2]_3$, is still a matter of controversy.[1] Whatever the basic composition of the crystal lattice, the myriads of microcrystals present an enormous and very active surface area to which carbonate, bicarbonate, phosphate, citrate, fluoride, sodium, magnesium, potassium and other ions are interchangeably attached in large and varying amounts. The mineral phase of bone is therefore not of fixed composition but varies somewhat from bone to bone and indeed from area to area in the same bone. It is markedly affected in both composition and structure by age, diet, disease, mechanical stress and many other factors.

Recent isotope studies of the surface chemistry

[1] This topic will be found discussed at length in the Transactions of the Fourth Conference on Metabolic Interrelations, Josiah Macy, Jr., Foundation, N. Y., 1952. For general summaries of this and related subjects see: ARMSTRONG, W. D., Phosphorus Metabolism, vol. 2, pp. 698–727, edited by McElroy and Glass, Baltimore, 1952, Johns Hopkins Press; and GUTMAN, A. B., *Bull. Hosp. Joint Dis.*, 12: 74–86, 1951.

of bone emphasize the rapidity and magnitude of the flow of ions between the solute phase of the intercellular fluid and the solid phase of the bone mineral. This ceaseless exchange chiefly involves the surface deposits of the bone mineral but also slowly effects recrystallization of the bone salt proper.[2] Thus bone mineral is constantly being deposited and resorbed. These processes normally are in nice dynamic equilibrium adapted to the needs of growth in the young and of bone repair in the adult.

Little is known about the detailed mechanisms of bone formation and even less about bone resorption. For many years it was assumed that calcification and decalcification could be regarded as relatively simple mass law phenomena entirely explicable in terms of $(Ca^{++})^3 \cdot (PO_4^{=})^2$ ion products. The blood plasma was believed normally to be supersaturated with respect to tricalcium phosphate, thus favoring precipitation of this salt; and if the serum calcium or inorganic phosphate level fell significantly, a state of undersaturation supervened and the bone salt went back into solution. It has since become apparent that the bone salt is not composed of $Ca_3(PO_4)_2$, a substance of doubtful occurrence formation of which would involve an improbable fifth order reaction; moreover, it is now clear that the blood plasma is not supersaturated with respect to the bone salt. More likely, at least from mass law considerations alone, would be the initial formation of secondary calcium phosphate, $CaHPO_4$, which is readily precipitated from solutions containing calcium and inorganic phosphate ions by a reaction of the second order. The presence of $CaHPO_4$ has not yet been conclusively demonstrated in bone, however, and its role in bone formation remains unsubstantiated.

While the deposition and resorption of the bone salt presumably must ultimately be governed by its solubility characteristics, it now seems unlikely that an acceptable theory of calcification and decalcification based solely on simple mass law considerations can be formulated within the framework of present knowledge. The composition of both solute and solid phase is too heterogeneous and variable; ion exchange, not definable in terms of the laws of mass action, plays too important a role; and there is a growing body of evidence for the participation of complex enzyme systems.

[2] Neuman, W. F. and Mulryan, B. J. *J. Biol. Chem.*, 193: 237, 1951; 195: 843, 1952.

Any satisfactory theory of calcification must take into account both humoral and local tissue factors. The importance of *humoral* factors is indicated by the disturbances in calcification of cartilage and osteoid encountered in such diseases as rickets and osteomalacia, characterized by hypophosphatemia. Deposition of bone salt requires appropriate concentrations of inorganic phosphate, calcium, bicarbonate, hydrogen and other ions in the blood plasma and intercellular fluids. This was well demonstrated almost thirty years ago by Shipley who showed that slices of rachitic rat cartilage would calcify *in vitro* when immersed in serum obtained from a normal growing child, and indeed in artificially prepared solutions of inorganic calcium and phosphate salts in equivalent concentrations, but not in serum obtained from a rachitic child and deficient in inorganic phosphate.

The importance of *local tissue* factors is indicated by the highly selective nature of the property of calcifiability. Deposition of bone salt occurs only in certain predisposed tissues and not in others even though all are bathed in intercellular fluid presumably of the same composition. The nature of these local tissue factors is still obscure. It is presumed that the predisposition to calcification is determined by specific cell activities, probably involving the action of enzymes.

To be sure, several groups of investigators have shown that bone mineral can be made to deposit selectively *in vitro* in cartilage or bone previously boiled or otherwise treated to inactivate the enzymes present. To accomplish this, however, requires immersion for long periods in solutions containing very high concentrations of calcium and inorganic phosphate, far beyond the physiologic range. To effect deposition of the bone salt in the presence of inorganic phosphate and calcium concentrations approximating those of normal plasma however, i.e., to build up the required local concentrations of phosphate and calcium in the face of unfavorable concentration gradients in the intercellular fluid, would appear to necessitate expenditure of energy and the operation of appropriate enzyme systems.

The first suggestion that enzymes might participate in the deposition of bone salt came some thirty years ago from Robison[3] who discovered the presence of alkaline phosphatase,

[3] Robison, R. *Biochem. J.*, 17: 286, 1923.

an enzyme which splits off inorganic phosphate from a variety of phosphoric esters, at sites of bone formation. Robison proposed that this enzyme brought about bone salt deposition by dephosphorylation of phosphoric esters there present, thus producing a local excess of inorganic phosphate ion which, with the calcium ions of the intercellular fluid, caused local supersaturation and consequent precipitation of bone salt. One difficulty with this view, recognized by Robison, was the apparent lack of significant amounts of phosphoric ester substrates in blood plasma and presumably in intercellular fluid. Moreover, Robison and Rosenheim[4] later found that *in vitro* calcification of cartilage could be blocked by iodoacetate, fluoride and cyanide in concentrations which did not inhibit alkaline phosphatase. The original theory was therefore modified to include a second mechanism, the nature and function of which were not clearly defined apart from some kind of presumed trigger action which accelerated the immediate deposition of the bone salt. Subsequent work has clarified the significance of the blocking effects of iodoacetate and fluoride.

It has been known ever since Claude Bernard's day that the deposition of bone mineral in calcifying cartilage is preceded by swelling of the cartilage cells to form "hypertrophic" cells and that this swollen appearance of the provisional zone of calcification is due in large part to the intracellular accumulation of glycogen. As noted by Creighton, Harris and others, these glycogen stores disappear just prior to or coincident with the appearance of bone salt in the adjacent cartilage matrix—a striking juxtaposition in time and place which indicated a possible interrelationship between glycogenolysis and calcification. Harris in 1932 suggested that hexosephosphoric esters formed from glycogen might provide the substrates for alkaline phosphatase required by the Robison theory of calcification.

While Harris' speculation does not presently appear to be correct, there is accumulating evidence that glycogenolysis is in some way essential for calcification in cartilage. Phosphorylase and the entire gamut of glycolytic enzymes and phosphoric ester intermediates have been shown to be present in calcifying cartilage.[5–7] Moreover, it has been found that if glycogenolysis is interrupted by suitable enzyme inhibitors, *in vitro* calcification of cartilage also is blocked[6,8]—thus explaining Robison's inhibition of calcification by iodoacetate and fluoride—but will proceed smoothly if any phosphoric ester ordinarily formed in glycolysis subsequent to the site of block is added to the calcifying solution. Prior removal of glycogen by incubation of cartilage slices with saliva (amylase) also inhibits calcification in solutions containing phosphorus as inorganic phosphate, and calcification is restored by addition of glucose-1-phosphate.[9]

Inhibition of *in vitro* calcification of cartilage by fluoride, which selectively inhibits enolase and the formation of phosphopyruvate from 2-phosphoglycerate, would seem to indicate that the esters of the glycogenolytic series are not dephosphorylated by phosphatase or other enzymes prior to phosphopyruvate formation. The further fate of the phosphoric (and pyruvic) acid moiety of phosphopyruvate, a critical step in bone salt formation, has not yet been traced. It may be presumed, from analogies with the glycolytic reactions in muscle and other tissues, that enzymatic transphosphorylation, to form such high energy phosphate compounds as ATP, follows. ATP has, indeed, been identified in calcifying cartilage[7] where it may serve as a source of both readily available energy and readily available phosphate. It has not been possible, however, to demonstrate that the phosphorus of ATP, which forms a relatively undissociated complex with calcium ions, is made available for bone salt formation, at least in the rat;[8,10] in sheep embryo cartilage, according to Cartier, ATP is so utilized. The penultimate phosphoric esters, from which the phosphorus of the bone salt presumably is finally derived, and the relevant mechanisms of phosphate transfer have not yet been defined.

While all these preparatory changes are

[4] Robison, R. and Rosenheim, A. H. *Biochem. J.*, 28: 684, 1934.

[5] Gutman, A. B. and Gutman, E. B. *Proc. Soc. Exper. Biol. & Med.*, 48: 687, 1941.

[6] Gutman, A. B., Warrick, F. B. and Gutman, E. B., *Science*, 95: 461, 1942.

[7] Albaum, H. G., Hirshfeld, A. and Sobel, A. E. *Proc. Soc. Exper. Biol. & Med.*, 79: 238, 682, 1952.

[8] Gutman, A. B. and Yü, T. F. Tr. Conf. Metabolic Interrelations, vol. 1, p. 11; vol. 2, p. 167. New York, 1949, 1950. Macy Foundation.

[9] Marks, P. A. and Shorr, E. *Science*, 112: 752, 1950.

[10] DiStefano, V. and Neuman, W. F. *J. Biol. Chem.*, 200: 759, 1953.

transpiring within the cartilage *cell*, apparently for synthesis of one or another high energy phosphate ester from the inorganic phosphate of the intercellular fluid, there are concomitant developments within the cartilage *matrix*, in which the bone salt proper is to be deposited. The acid mucopolysaccharides of the matrix about to undergo calcification appear to lose their metachromatic staining properties. The significance of this is not altogether clear but loss of metachromasia under these circumstances probably is due more to preferential binding of calcium ions, in competition with dye, then to depolymerization of chondroitin sulfate complexes. In any event, as Boyd and Neuman[11] have established, the strongly acidic chrondroitin sulfates of cartilage matrix act much like a cation exchange resin in preferentially binding calcium and thus effect the necessary increase in concentration of calcium at the site of calcification.

At some point in these proceedings, perhaps coincident with dissolution of the cartilage cell, the processes in the cartilage matrix and cartilage cell merge, with transfer of phosphorus, in a form and by mechanisms not yet defined, to the matrix. It is possible that a large molecular complex containing collagen, chondroitin sulfates, calcium and phosphorus is thus formed from which, by molecular rearrangements, the ultimate bone apatite is separated, perhaps by way of secondary calcium phosphate. In any event, such is the sense of the findings of Freudenberg and György[12] who, in 1923, schematically represented their observations as a repetitive cycle of three steps: (1) binding of calcium ions by the organic ground substance; (2) binding of phosphate (or bicarbonate) ions of the interstitial fluid by the ground substance so that a calcium-phosphate (or carbonate)-protein complex is formed; (3) splitting off of calcium phosphate (or carbonate) from this complex, thus freeing the calcium binding groups of the ground substance to initiate the cycle again. That calcium is fixed by the cartilage ground substance prior to incorporation of phosphate was confirmed by Boyd and Neuman.[11]

The place of phosphatase in this schema is not evident and, indeed, the presumptive role of this enzyme in the processes of calcification is still quite obscure. Recent experiments with beryllium, a potent alkaline phosphatase inhibitor, indicate that *in vitro* calcification of cartilage is blocked when phosphorus is supplied as phosphoric ester (beta-glycerophosphate) but not in the presence of inorganic phosphate—implying that alkaline phosphatase may not be essential for the later stages of calcification under conditions approximating those *in vivo*.[13] McLean has suggested that the chief role of this enzyme may be in the synthesis of the fibrous proteins of the matrix and has to do with acquisition of the property of calcifiability. Alkaline phosphatase may also operate in its newly discovered capacity as a transphosphorylase, as well as a dephosphorylase. These possibilities are all in the realm of conjecture.

It is apparent that our knowledge of the mechanisms by which the bone salt is formed, deposited and resorbed is still fragmentary and many important segments are still highly speculative. Moreover, the schema proposed applies only to endochondral calcification and may have little or no bearing upon the mechanisms of bone formation elsewhere. Finally, the effects of various hormones and vitamins, which are well known to exert an important influence on bone metabolism, are not accounted for.

Dr. Plimpton: With this background covering the nature of bone and the mechanisms of calcification, we can go down now from the Hill of Difficulty into the Valley of Humiliation and discuss some of the factors which influence serum calcium and phosphorus levels and bone metabolism. There are many, but we will limit our attention to the more important ones. In Table 1 they have been divided arbitrarily into groups on the basis of how much is known about their mechanisms of action.

The parathyroid glands are like the islet cells of the pancreas in that there is no known tropic hormone. Their activity seems to be regulated largely by the level of serum calcium. A low serum calcium stimulates them to secrete, and a high serum calcium depresses their activity. A high serum phosphorus has been thought to stimulate the parathyroid glands but this is probably only through secondary lowering of the serum calcium. In those studies in which

[11] Boyd, E. S. and Neuman, W. F. *J. Biol. Chem.*, 193: 243, 1951; Tr. Conf. Metabolic Interrelations, vol. 4, p. 100. New York, 1952. Macy Foundation.

[12] Freudenberg, E. and György, P. *Biochem. Ztschr.*, 142: 407, 1923.

[13] Yü, T. F. and Gutman, A. B. *Proc. Soc. Exper. Biol. & Med.*, 75: 481, 1950; Tr. Conf. Metabolic Interrelations, vol. 3, p. 90; New York, 1951; Macy Foundation.

the serum phosphorus was raised, and then the serum calcium maintained, as in the work of Ham et al.[14] or Stoerk and Carnes[15] there was no hypertrophy of the parathyroid glands. Other changes, as in blood pH, have no direct effect on the parathyroid glands.

Parathyroid hormone is a protein which has not as yet been too well characterized. L'Heureux et al.[16] have shown that commercially available parathyroid hormone is heterogeneous with at least two components on electrophoresis. There are also two main actions of parathormone which seem to be distinct. Parathyroid hormone can cause a phosphate diuresis by the kidney, and it can also cause direct resorption of bone. Perhaps there are two parathyroid hormones, but until there is better characterization this assumption would probably not serve any useful purpose.

Many years ago Albright[17] showed that when a hypoparathyroid individual was given an injection of parathormone a phosphate diuresis was the first thing to follow. This occurred in the first few hours, and could be demonstrated regularly only in hypoparathyroid patients who had a high serum phosphorus to start with. In normal people there is only an inconsistent effect on phosphate. The mechanism by which this change in tubular phosphate transport is accomplished is obscure. Those observers, like Pitts, who have been able to demonstrate a phosphate Tm have been unable to demonstrate any effect of parathormone. On the other hand, many observers who could not demonstrate a phosphate Tm could nevertheless show a depression of phosphate reabsorption by parathormone. Sirota[18] recently determined simultaneously the renal clearances of inulin, p-amino hippurate, inorganic phosphate and $TmPO_4$ in two adult male subjects with hyperparathyroidism before and after removal of their parathyroid adenomas. A marked reduction in renal tubular phosphate reabsorption was observed preoperatively. After removal of the adenoma there was improvement in phosphate reabsorption at all measured phosphate loads with no change in glomerular filtration rate. This would appear to be fairly substantial evidence for the action of parathormone on renal tubular phosphate transport mechanisms.

The other action of parathormone is to cause direct resorption of bone. This was shown independently by Selye, Albright and Stoerk to occur even in the absence of the kidneys. More recently Barnicot[19] has transplanted parathyroid glands in contact with bone into another animal, and noted resorption of the transplanted bone only on the side in contact with the parathyroid gland. This did not occur with other tissues, and would indicate a direct action on bone. There may be a clue to the site of action of parathormone on bone in the work of Carnes.[20] He used rachitic animals which have a great deal of uncalcified matrix and was able to show that parathormone caused a resorption of matrix. This suggests that perhaps parathormone acts primarily on the matrix, and that with removal of matrix the mineral salts are resorbed concomitantly. Also in support of the action of parathormone on the matrix is the observation of Engel[21] that there is a five-fold increase in the circulating mucopolysaccharide, expressed as tyrosine or carbohydrate, after an injection of parathormone. This may be a reflection of the mobilization of matrix.

The absolute blood levels and over-all metabolic balances of calcium and phosphorus are obviously important in the metabolism of bone. In a general sense, the maintenance of normal bone structure depends on a product of serum calcium (10 mg. per cent) times serum phosphorus (4 mg. per cent) equal to about 40. With products much less than 40, the bones are poorly mineralized, as in rickets of the low calcium or low phosphorus variety. With values much over 40, there is danger of metastatic calcification of the soft tissues. Raising the serum phosphorus by intravenous infusion of phosphate causes a fall in the serum calcium, due to the formation of a colloidal calcium-phosphate complex which can be visualized in the macrophages. With a fall in serum calcium the secretion of parathormone is increased, phosphate is diuresed, calcium is mobilized from bone and the serum calcium level returns toward normal. On

[14] Ham, A. W., Littner, N., Drake, T. G. H., Robertson, E. C. and Tisdall, F. F. *Am. J. Path.*, 16: 277, 1940.

[15] Stoerk, H. C. and Carnes, W. H. *J. Nutrition*, 29: 43, 1945.

[16] L'Heureux, M. V., Tepperman, H. M. and Wilhelmi, A. E. *J. Biol. Chem.*, 168: 167, 1947.

[17] Albright, F. and Reifenstein, E. C. The Parathyroid Glands and Metabolic Bone Disease. Baltimore, 1948. Williams & Wilkins.

[18] Sirota, J. H. *Federation Proc.*, 12: 133, 1953.

[19] Barnicot, N. A. *J. Anat.*, 82: 233, 1948.

[20] Carnes, W. H. *Am. J. Path.*, 25: 736, 1950.

[21] Engel, M. B. *Arch. Path.*, 53: 339, 1952.

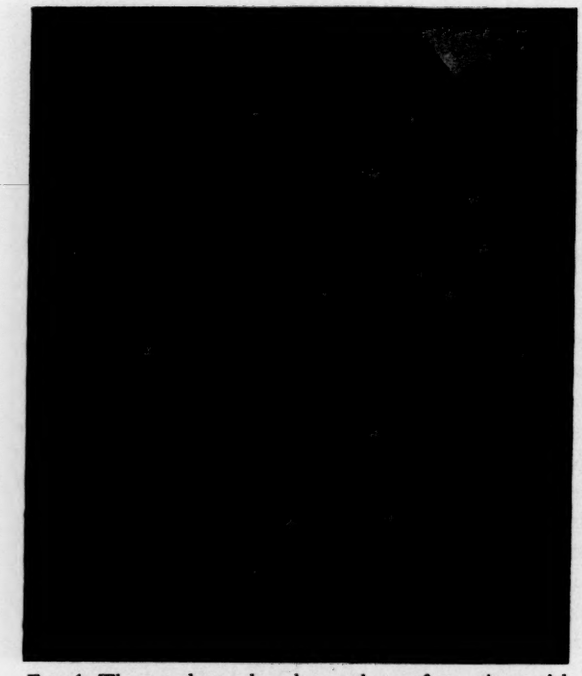


FIG. 1. The two lower hands are those of a patient with acromegaly and are seen to be enlarged when compared with a normal control (above). The right hand of the acromegalic is larger than the left, however, due to the presence of multiple arteriovenous aneurysms.

the other hand, infusions of calcium cause a rise in serum phosphorus. With the rise in serum calcium parathyroid activity is diminished, phosphate excretion is decreased, and hence the serum phosphorus starts to rise. There have recently appeared several reports, such as those of Burnett[22] and Wermer,[23] indicating the perils of long-continued excess calcium ingestion, especially in association with large amounts of alkali. As one might expect, severe metastatic calcification results. In Wermer's case there was dramatic resorption of large calcific masses when the calcium and alkali intake was restricted.

Vitamin D acts in three main ways. It increases the absorption of calcium directly from the intestines, and perhaps secondarily the absorption of phosphorus. How this is accomplished is unknown. In toxic doses vitamin D not only causes such high serum calcium levels that metastatic calcification occurs, but also causes bone resorption associated with a rise in serum alkaline phosphatase. This response to excessive vitamin D intake has been demonstrated even when the diet was free of calcium. Finally, Albright has some evidence that large doses of vitamin D given to a hypoparathyroid patient may lead to a phosphate diuresis, although of much smaller magnitude than seen with parathormone.

The effects of activity and circulation are best discussed together since it is very difficult to separate them. It is well known that when limbs are put to rest in a cast, or by paralysis, there is demineralization of the bone. It is also known that when bone is laid down, it is laid down along lines of stress. When complete rest is imposed on a bone there is no longer any stress to stimulate the formation of new bone, and if resorption continues at the same rate there will be demineralization. But this same rest also decreases the circulation. And it is well known that increasing the circulation leads to hypertrophy of the bone and soft tissue of an extremity. Patients with multiple arteriovenous aneurysms of an extremity frequently have hypertrophy of that extremity. Here (Fig. 1) is a man with acromegaly, and his left hand is obviously larger than the normal control, thus indicating some of the effects of growth hormone. But his right hand is even larger than his left, with dilated veins and increased heat. He has in his right arm multiple arteriovenous aneurysms. This is an example of the importance of circulation. Almost all of the effects of immobilization can be prevented by placing the patient on an oscillating bed. But here again it is hard to tell whether one is increasing the stress, improving the circulation, or both. In general, the most outstanding feature of lack of stress is demineralization, whereas the most outstanding feature of circulation is that with increased circulation there is a tremendous overgrowth of bone and other tissues. Unfortunately, the mechanism by which either of these effects is mediated is as yet unknown.

If we turn now to the next group of agents which influence calcium, phosphorus or bone metabolism (Table 1), we are further humbled. Growth hormone certainly extends the length of bones with ununited epiphyses. There seems to be a stimulation of the osteoblasts, with a slight rise in the serum alkaline phosphatase and serum phosphorus. At least this is the explanation given for the slightly higher serum phosphorus seen in growing children and acromegalics. But so far, even with the purest growth hormone available, these effects have

[22] BURNETT, C. H., COMMONS, R. R., ALBRIGHT, F. and HOWARD, J. E. *New England J. Med.*, 240: 787, 1949.

[23] WERMER, P., KUSCHNER, M. and RILEY, E. A. *Am. J. Med.*, 14: 108, 1953.

not been produced in man and the precise details of the naturally observed actions of growth hormone are still obscure. Becks et al.[24] have found that in hypophysectomized animals ACTH largely counteracts the effect of growth hormone.

TABLE I
AGENTS AFFECTING THE METABOLISM OF CALCIUM, PHOSPHORUS AND BONE

A. Something Is Known of Mechanism	
1. Parathyroid glands	3. Vitamin D
2. Calcium, phosphorus	4. Circulation, activity
B. Little Is Known	
1. ACTH	4. Starvation
2. Cortisone	5. Acidosis
3. Growth hormone	6. Beryllium
C. Less Is Known	
1. Estrogens	4. Vitamin C
2. Androgens	5. Vitamin A
3. Thyroid	6. Strontium

ACTH and cortisone may cause demineralized bones in man even when other causes, such as immobilization, have been eliminated. Osteoporosis is also seen not infrequently in Cushing's syndrome. It has been thought that this was due to deficient osteoid or matrix formation, perhaps secondary to the general negative nitrogen balance, and perhaps due to some specific effect on matrix itself. The negative nitrogen balance accompanying cortisone administration has been elegantly studied by Hoberman[25] and others. It seems to be due to an anti-anabolic effect on amino acids forming proteins, as well as to increased catabolism. There is also the experimental demonstration of decreased mucopolysaccharide formation in experimentally produced fractures of animals treated with cortisone, as reported by Blunt and others.[26] But although these results are suggestive, it is very difficult in an experimental animal, or even in a rachitic animal with lots of uncalcified matrix, to demonstrate any effect of cortisone on matrix which is not similar to that of starvation. And since, in our own experience cortisone-treated animals all seem to lose weight, it is hard to know whether to ascribe the observed effects to the starvation or to the cortisone. Starvation obviously can cause osteoporosis through a loss of protein, and the matrix would suffer along with the rest of the body. If there were also a deficiency of minerals and vitamins, one would expect a mixed picture.

Acidosis has frequently been described as a cause of demineralization of bone. Obviously, this is not due to any direct effect on bone since it is not possible to get the pH of the circulating fluids sufficiently low. The mechanism would be through the mobilization of calcium as a fixed base to spare sodium and potassium. The parathyroid glands presumably would respond to a lowered serum calcium by mobilizing more bone salt. If the parathyroids are removed and a bilateral nephrectomy is done, the bones remain almost normal despite considerable acidosis. On the other hand, if the parathyroids are left in and the kidneys are removed, the acidosis persists and the bones are also demineralized. It is therefore likely that the demineralization occurring in acidosis is mediated by parathyroid hyperactivity.

Other agents, such as estrogens, androgens, thyroid, vitamin C and vitamin A, may produce definite effects but the mechanism of their action is obscure. Dr. Pines will tell you what is known about them when he discusses their clinical use.

I would like to turn your attention to one of the more recent and exciting aspects of calcium metabolism. More and more commonly we are seeing patients whose main disability is due to hypercalcemia. This is usually due to metastatic neoplastic disease. In some of these cases the symptoms of hypercalcemia may be more prominent than those of the underlying disease. The symptoms of hypercalcemia are (1) lassitude and weakness; (2) nausea, vomiting and constipation; (3) polyuria and polydipsia; (4) coma; (5) renal calculi and nephrocalcinosis; (6) metastatic calcification in stomach, lungs, bursae and kidneys. Obviously there are many causes for these symptoms. A brief differential diagnosis would include such things as primary and secondary hyperparathyroidism, vitamin D toxicity, excess calcium and alkali ingestion, immobilization, multiple myeloma, metastatic malignancy with or without hormone therapy, and finally such things as sarcoid or acute leukemia.

In order to separate these possibilities one obviously needs the usual good history and physical examination and, in addition, Bence Jones protein determination, plasma protein partition, serum urea and carbon dioxide content, bone marrow aspirations, and skeletal

[24] BECKS, H., SIMPSON, M. E., MARX, W., LI, C. H. and EVANS, H. M. *Endocrinology*, 34: 311, 1944.

[25] HOBERMAN, H. *Yale J. Biol. & Med.*, 22: 341, 1950.

[26] BLUNT, J. W., PLOTZ, C. M., LATTES, R., HOWES, E. L., MEYER, K. and RAGAN, C. *Proc. Soc. Exper. Biol. & Med.*, 73: 678, 1950.

roentgenograms including the lamina dura. Of course, the crux of the matter lies in the serum calcium, phosphorus and phosphatase values. To assist in separating the various entities, this graph has been prepared. (Fig. 2.) The lines are meant to represent boundaries between areas. Thus a case of hyperparathyroidism might start out with a very high serum calcium and a very low serum phosphorus, and be up in the high left hand corner of the graph. As the disease progressed, with increasing renal damage the phosphorus would tend to rise, the calcium to fall, and the case would approach the area of secondary hyperparathyroidism.

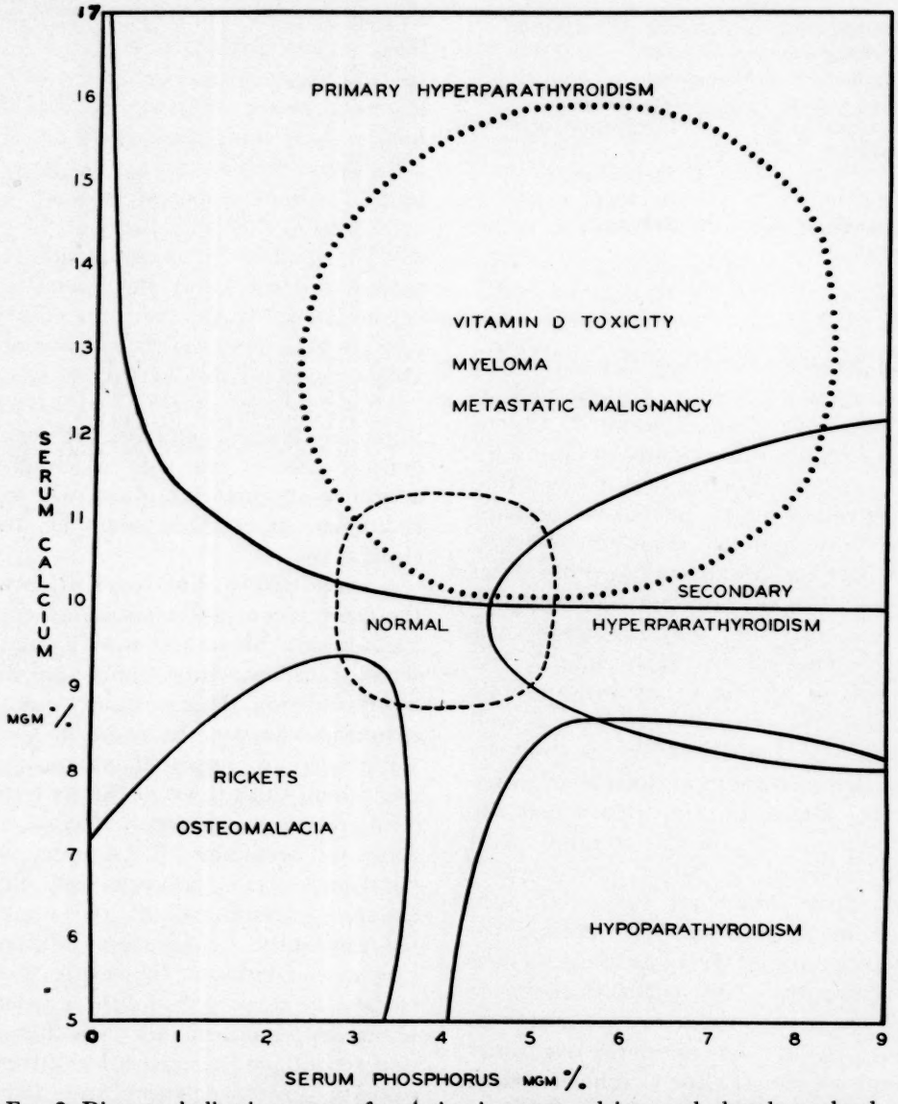
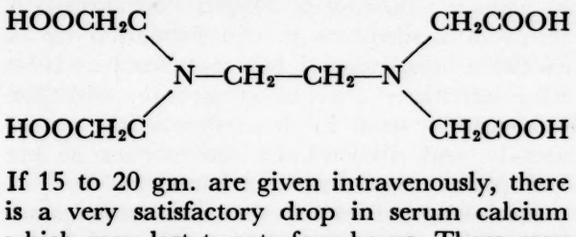


FIG. 2. Diagram indicating range of variation in serum calcium and phosphorus levels in normal subjects and in various disorders affecting calcium and phosphorus metabolism.

It will be noted that there is a large area of overlap where it is impossible to distinguish between primary or secondary hyperparathyroidism, or myeloma or metastatic malignancy on the basis of calcium alone. Cases that fall in this group are always being discussed at grand rounds. Sometimes even with all the ancillary evidence it is still impossible to tell in which group the case belongs, and occasionally the discreet approach may be to explore the neck and mediastinum in the hope of finding a remediable lesion like a parathyroid adenoma.

In cases in which the primary cause of hypercalcemia is not directly susceptible to treatment,

and in which it is the disabling feature, the hypercalcemia *per se* may require symptomatic treatment. In the past we have been able to offer only rehydration, and occasionally an exchange transfusion with bank blood or blood which has been decalcified by being run through a resin column. Recently it has been possible to use ethylene diamine tetraacetic acid as a chelating agent for reducing the serum calcium. This substance, which is called "Versene" or "Sequestrene," has this formula:



If 15 to 20 gm. are given intravenously, there is a very satisfactory drop in serum calcium which may last twenty-four hours. There may be rapid clearing of those symptoms due to hypercalcemia. The only toxic reaction so far observed is severe hypocalcemia if too much is given. The permanent place of this agent in therapy is obviously undetermined, and it is only a research tool at the moment. But it looks promising and it seems fair to call your attention to it.

We have now more than a little background and it is time to turn to the goal for which every pilgrim strives. I refer, of course, to the Delectable Mountains, and Dr. Kermit Pines will assume the role of Mr. Greatheart and guide you to them with a discussion of osteoporosis, osteomalacia and osteitis fibrosa.

Dr. Kermit L. Pines: In discussing abnormalities of bone metabolism, I shall limit myself to certain disorders of the skeleton of which enough of the pathogenesis is understood to permit rational, if not always effective, management. In this category one may certainly include generalized osteitis fibrosa due to hyperparathyroidism, osteomalacia and osteoporosis. Osteoporosis is probably the most common medical disease of bone we encounter in this Hospital and will be the major subject of my discussion today. I shall also describe briefly an unusual type of osteomalacia due to renal tubular acidosis, a condition which we have had occasion to study in some detail.

Osteitis fibrosa generalisata is caused by increased resorption of bone salts and destruction of the matrix due to overactivity of the parathyroid glands. The classical picture of hyperparathyroidism is familiar to you and presents no serious diagnostic problem. The difficulty lies in recognition of the disorder in its earlier stages, particularly in patients who present with renal calculi but without significant skeletal changes. Most patients admitted to this Hospital with renal stones have routine serum chemistry studies done to exclude hyperparathyroidism. In a small but significant percentage of these cases, such determinations lead to the recognition of underlying parathyroid dysfunction in advance of the appearance of systemic changes. In evaluating such patients with borderline findings additional studies are often helpful. The Sulkowitch qualitative test for urinary calcium may be strongly positive in hyperparathyroidism even without unequivocal elevation of the serum calcium level. More significant is a marked elevation of the twenty-four-hour urinary calcium excretion after one week on a low calcium intake.

When the diagnosis of hyperparathyroidism can be made with assurance, surgical removal of the offending tumor should follow without delay. When the diagnosis cannot be excluded in equivocal cases, further observation is often indicated and exploration of the neck sometimes should be performed even when there is reasonable doubt.

Osteomalacia, it is generally agreed, is characterized by inadequate deposition of bone salts in the osteoid matrix owing to a deficiency of calcium and/or phosphorus in the serum. The uncalcified osteoid, produced by the osteoblasts at a normal or increased rate, is clearly visible in histologic preparations. *Osteoporosis* is believed by many to represent a defect in production of osteoid or bone matrix, thus providing an abnormally limited area for the deposition of bone salts. In sections, a decreased number of osteoblasts or histochemically abnormal osteoblasts are seen. Osteoporosis, then, appears to be a tissue, rather than a mineral, disorder. The causes of osteoporosis are listed in Table II taken from the monograph by Albright and Reifenstein,[17] with minor modifications.

Disuse atrophy occurs in bone as in other tissues. It is important to remember that it may complicate the picture of any bone disease. In the presence of rapid turnover of bone, such as occurs in Paget's disease, or in growing children, immobilization may lead to marked hypercalcemia. Even in normal adult bone, however, atrophy of disuse may be followed by slight

elevations of the serum calcium, increases in urinary calcium and the formation of renal calculi.

Estrogen deficiency is highly controversial as a cause of osteoporosis. Many investigators reject it in their capacity as scientists, while using estrogens routinely in their role as clinicians. There is considerable evidence to support Albright's view that osteoporosis occurring in women after the menopause results from decreased secretion of estrogens. There is adequate confirmation of the retention of bone salts with estrogen administration to patients, as well as in certain species of experimental animals. On the other hand, replacement therapy has not produced unequivocal x-ray improvement even after years; and, in a single reported case, no change was seen in a bone biopsy after six months of continuous treatment. Postmenopausal osteoporosis is a definite clinical entity. Until a better explanation is offered, I shall continue to accept estrogen deficiency as the cause, at least as a working hypothesis.

TABLE II
CAUSES OF OSTEOPOROSIS
(After Albright and Reifenstein[17])

I. Decreased osteoblastic activity
   A. Disuse atrophy (immobilization)
   B. Estrogen deficiency
   C. Congenital (osteogenesis imperfecta)
II. Defective or inadequate matrix
   A. Androgen deficiency
   B. Vitamin C deficiency
   C. Excess adrenal cortical steroids (11-oxysteroids)
   D. Protein lack (absorptive defect or dietary)
III. Unclassified. Thyrotoxicosis, acromegaly, diabetes mellitus

The third cause of decreased osteoblastic activity is congenital. In osteogenesis imperfecta, the disease of fragile bones and blue sclerae, there seem to be enough osteoblasts. The trouble is that they do not, for obscure reasons, perform their function adequately, at least until the patient reaches maturity.

Before proceeding to the second category of causes of osteoporosis, defective matrix, I should say that the separation of osteoblast function from the quality or amount of bone matrix formed is somewhat artificial. It is useful in pointing up similarities and differences but is not, to my knowledge, based on any extensive scientific data. For example, ground substance is defective or absent in scurvy; at the same time, however, the osteoblasts, show distinct changes, both morphologically and chemically, according to Follis.[27] At any rate, deficiency of androgens is presumed to account in part for the osteoporosis that occurs in elderly patients who do not qualify for the diagnosis of postmenopausal osteoporosis. The widespread connective tissue disorder in Cushing's syndrome affects bone as well, and Demartini, Grokoest and Ragan[28] have recently demonstrated that even this unpleasant aspect of hyperadrenalism can be reproduced by administration of cortisone. Whether the so-called hunger osteopathy seen in Europe following prolonged starvation is a result of inadequate matrix formation or of excessive bone resorption is not clear; and the same questions arise in connection with the osteoporosis seen in hyperthyroidism, acromegaly and diabetes, or osteoporosis of the "idiopathic" variety, which I have not listed.

Reviewing the various causes of osteoporosis, it is obvious at once that more than one factor may be operating in any given situation. The clinical picture of osteoporosis varies, of course, with the cause. The common types are associated with bone pain, particularly over the spine and pelvis, often referable to compression fractures. The pain may become sufficiently severe to keep the patient in bed, leading to the superimposition of disuse atrophy. The x-ray picture is often characteristic in that demineralization may be limited to the spine and pelvis, sparing the skull and extremities for the most part. Not infrequently, however, the entire skeleton will show marked thinning. Even in these patients the dental lamina dura is usually preserved. Compression fractures of the spine are frequent and are often the acute episode which leads the patient to seek medical attention.

Since osteoporosis is a tissue, not a mineral, disorder the serum calcium, phosphorus and alkaline phosphatase levels should be within normal limits, and they are as a rule. When the disease is rapidly progressive the serum calcium may rise but this rarely occurs. The serum alkaline phosphatase may at times be slightly elevated, perhaps in association with the multiple fractures that often occur.

The treatment of osteoporosis is not the most dramatically successful in modern medicine. Positive calcium balance and clinical improvement have been reported following the use of

[27] FOLLIS, R. H., JR. Tr. Conf. Metabolic Interrelations, vol. 2, p. 253. New York, 1950. Macy Foundation.

[28] DEMARTINI, F., GROKOEST, A. W. and RAGAN, C. *J. A. M. A.*, 149: 750, 1952.

high calcium diets in conjunction with the administration of vitamin D. The use of estrogens in the treatment of postmenopausal osteoporosis was first recommended by Albright and Reifenstein. They also found this treatment effective, at least in balance studies, in senile and other types of osteoporosis. Although estrogens alone produce a positive calcium balance, addition of androgens increases the effect. Clinically, most observers agree that symptomatic relief is the rule within a few weeks after starting this regimen. The patient may throw away her brace and return to a relatively active life, which in itself may lead to further improvement. Although the x-rays show no change, the patient behaves as though she were unaware of the radiologist's opinion.

The doses used are 0.5 to 1.0 mg. of stilbestrol (or equivalent doses of other estrogens) daily and 20 to 50 mg. of methyltestosterone daily or an equivalent dose of testosterone propionate parenterally. To minimize the danger of overstimulation of the uterus the hormones are omitted for seven to ten days every four to six weeks. This may lead to withdrawal bleeding. It is also advisable to have the patient evaluated every four to six months by a gynecologist to exclude the possibility of uterine carcinoma. The diet should be high in protein.

In most patients these doses of androgens will produce masculinization after variable periods. This is readily reversible by discontinuance of the medication. Salt and water accumulation is seen occasionally; salt restriction may be of value in these patients. Nausea and vomiting associated with stilbestrol may be severe. This symptom may be relieved by changing to another estrogen.

Shorr[29] recently suggested the use of strontium in the treatment of osteoporosis. Strontium appears to be interchangeable with calcium in respect to deposition of bone salts. Balance studies in patients with osteoporosis have shown that addition of strontium to a high calcium intake leads to retention of a greater amount of calcium plus strontium than is possible with calcium alone. In some patients the clinical response is dramatic, relief of pain beginning within two to forty-eight hours of the start of treatment. In practice, most patients on the strontium regimen are also given estrogens and androgens, which appear to increase the total retention of calcium and strontium. The dose of strontium lactate used is about 7 gm. daily.

Few generalizations can be made about the use of orthopedic supports. They should certainly be avoided in the routine management of these patients in order to prevent the superimposition of disuse atrophy. In some patients, particularly following compression fractures, a brace may afford relief unobtainable otherwise. Nevertheless, a brace should be considered a temporary measure.

The differential diagnosis of osteoporosis depends largely upon the x-ray picture. Demineralization often affects the spine and pelvis predominantly. Hyperparathyroidism and osteomalacia are readily excluded by the essentially normal serum values for calcium, phosphorus and alkaline phosphatase. Metastatic neoplasm to bone is rarely so diffuse. Multiple myeloma, however, may on occasion present a difficult problem in differential diagnosis. Usually, however, urine examination for Bence Jones protein, serum protein partition and marrow aspiration make the diagnosis clear.

Osteomalacia, you will recall, is a mineral disorder. In contrast to osteoporosis, osteoblastic activity is normal or even increased. Here the demineralization results from inadequate deposition of bone salts because of insufficient quantities of calcium and/or phosphorus in the circulating blood. The serum phosphorus is usually reduced, the serum calcium is low normal or low, and the alkaline phosphatase is elevated. Of interest in this respect is the finding of "pseudo-fractures," linear areas of decalcification, often multiple and symmetrical, prior to the appearance of generalized demineralization. This syndrome, to which the name of an American radiologist, Milkman, has been given, is pathognomonic of osteomalacia. Le May and Blunt of this hospital have suggested an ingenious explanation for these pseudo-fractures.[30] They pointed out that all the reported locations for these lesions are in the vicinity of blood vessels, raising the question of erosion by these vessels as a possible cause.

Of the many causes of phosphorus and calcium deficiency in the serum, one of the most interesting is renal tubular acidosis. This disorder was first described in 1936 by Butler,

[29] SHORR, E. and CARTER, A. C. Tr. Conf. Metabolic Interrelations, vol. 1, p. 144. New York, 1950. Macy Foundation.

[30] LEMAY, M. and BLUNT, J. W. *J. Clin. Investigation*, 28: 521, 1949.

Wilson and Farber,[31] but was not well understood until Albright and his group[32] reported their studies in 1940 and 1946. In this disorder renal tubular excretion of hydrogen ion and ammonia is impaired, with maintenance of a nearly normal glomerular filtration rate. Since conservation of base depends upon these tubular mechanisms, fixed base is lost. Sodium and water are lost initially, but acute salt depletion has not been described. Low serum potassium is a frequent finding and several cases of paralysis from this cause have been seen. Phosphorus is lost with the calcium, possibly in response to secondary parathyroid stimulation as suggested by Albright, and the typical serum findings of osteomalacia appear. Besides the low phosphorus, the low normal calcium and the elevated phosphatase, the serum potassium is low normal or reduced, the serum bicarbonate is low, the serum chloride elevated and the NPN essentially normal. Because of the inability of the tubules to excrete acid the urine is neutral or alkaline. Table III summarizes the findings in seventeen patients with this rare disorder, including three patients studied at this hospital with Dr. Gilbert Mudge.

TABLE III

SYMPTOMS AND FINDINGS IN SEVENTEEN PATIENTS* WITH RENAL TUBULAR ACIDOSIS AND OSTEOMALACIA

Clinical Findings	
Weakness	10
Gait disturbance	10
Bone pain	9
Polyuria	9
Renal colic	6
X-ray Findings	
Nephrocalcinosis	12
Renal calculi	12
Generalized demineralization	11
"Pseudofractures"	10

* Females 13, males 4. Mean age, 27 yr., spread, 10–49 yr.

Studies on renal carbonic anhydrase by Pitts and by Berliner and their respective associates indicate that a deficiency of this enzyme in the renal tubule may account for the entire picture. Berliner has, in fact, produced a similar renal defect experimentally by administration of #6063, a sulfonamide derivative that is a powerful carbonic anhydrase inhibitor. What causes this relatively specific tubular defect in patients is not clear. Pyelonephritis often produces tubular damage in advance of significant glomerular damage, and preceded the onset of the disorder in one of our patients.

The treatment recommended by Albright and his co-workers is both logical and effective: alkali to compensate for the loss of base, and vitamin D and a high calcium diet to hasten the accumulation of calcium. Clinical improvement is marked within a few weeks, and remineralization of the bones is demonstrable in a matter of months. Careful management of the urinary tract infections that so often accompany renal calcification is essential. Two of our patients have now been followed for five years and have been free of symptoms, except for infrequent bouts of renal colic or acute urinary tract infections.

[31] BUTLER, A. M., WILSON, J. L. and FARBER, S. *J. Pediat.*, 8: 489, 1936.

[32] ALBRIGHT, F., BURNETT, C. H., PARSON, W., REIFENSTEIN, E. C., JR. and ROOS, A. *Medicine*, 25: 399, 1946.

SUMMARY

DR. GILBERT H. MUDGE: In this clinic we have considered some of the biochemical and physiologic aspects of bone, as well as some of the clinical disorders associated with abnormal patterns of bone metabolism. Considerable emphasis has been placed upon those conditions which are potentially reversible when the nature of the basic disturbance is determined.

From a functional point of view, bone may be regarded as a two-phase system composed of the matrix, mostly protein and mucopolysaccharides, and secondly, the bone salt, mostly calcium in association with several anions. Although the exact chemical nature of the calcium salt has not been determined, it has become increasingly clear that the component minerals are in a constant state of dynamic exchange between the ambient fluids and the solid bone salt. The process of ossification has been discussed from the chemical point of view. It was formerly thought that the deposition of bone could be accurately described by considering the solubility of the various salts in terms of the law of mass action. However, critical studies indicate a far more complicated process, and in recent years attention has been focused upon enzymatic reactions. Osseous phosphatase was the first enzyme to be examined; more recently the process of ossification has been studied in relation to the reactions of anaerobic glycogenolysis. Inhibitors of this metabolic pathway prevent normal bone formation but it is not yet possible to describe the formation or deposition of bone salt in terms of specific chemical or enzymatic reactions.

The physiology of the parathyroid hormone

has been reviewed. Its effect on bone is associated with two well documented actions: first, an apparently direct action on the kidney resulting in phosphaturia and, secondly, a direct lytic action on bone. Some evidence suggests that the latter effect may be primarily on the bone matrix. The effects of other factors on the metabolism of bone are also reviewed. These include vitamin D, the role of the circulation and of physical activity, and the effects of other hormones. It is emphasized that maintenance of the normal composition of bone results from the interaction of multiple factors. For example, demineralization secondary to acidosis must be evaluated in terms of the contribution of the parathyroid glands as well as in terms of renal function.

The clinical features of hypercalcemia are discussed. Of current interest are the dramatic results which have been obtained by the administration of the chelating agent, ethylene diamine tetraacetic acid, which causes a precipitous fall in serum calcium. However, experience with this compound is still limited and its eventual usefulness remains to be evaluated.

The commoner disorders of bone metabolism are presented in detail, and these include hyperparathyroidism, osteoporosis and osteomalacia. Although severe hyperparathyroidism presents a classic picture, there are many early cases which are equivocal and some of the problems in their management are emphasized. Osteoporosis is primarily a defect in bone matrix and can result from many causes. Similarly, osteomalacia, the primary deficiency of bone salt, has multiple etiologic factors. The management of these problems is considered in terms of the underlying causes. Special emphasis has been given to the somewhat debatable role of the sex hormones. The osteomalacia due to renal tubular acidosis, although rare, is worthy of note because of the very satisfactory results obtained with simple but appropriate therapy.

Clinico-pathologic Conference

Bronchial Asthma

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D. and David E. Smith, M.D. of weekly clinico-pathologic conferences held in the Barnes Hospital, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, B. G. (No. 210826), was a white truck driver, forty-nine years of age, who was admitted to the Barnes Hospital for the first time on June 10, 1952, because of asthma. The family history was negative. The past history was of interest in that the patient had had intermittent sinus trouble since 1936, his symptoms having come on two years after he went to work in a cement plant where he was exposed to dust. He worked in the plant for six years and then left that job to work as a truck driver. Except for the fact that he had been a heavy cigarette smoker for years, there was no other significant history; he had never had any known allergy.

In January, 1951, the patient developed an illness characterized by general myalgia, chilly sensations and malaise. He continued to work but several weeks later developed a cough productive of yellow non-bloody sputum. He was first told that he had influenza and subsequently that he had pneumonia; for the latter he was given aureomycin by his physician and his symptoms cleared promptly. The patient then felt well until June, 1951, when he developed a chronic, hacking cough which was worse at night and in the early morning. The cough was productive of very little sputum. Two months later he began to have paroxysms of choking and wheezing respirations; he was hospitalized in his home community, and responded rapidly to therapy which included intravenous and intramuscular injections and oxygen by mask. In the following months the patient was re-hospitalized on several occasions for similar symptoms, and each time his response to therapy was apparently good. On at least several occasions he received penicillin and streptomycin intramuscularly and penicillin orally. He was told that he had asthma and advised to use bronchodilators orally and by inhalation. On this regimen he was able to control his symptoms moderately well. He stated that he had never suffered exacerbation of asthma except during or just following an upper respiratory infection.

Late in 1951 the patient consulted a physician who obtained various roentgenographic studies. The patient was told that he had sinus trouble and "enlarged bronchial tubes." Because of the increasing frequency of the asthmatic attacks and their progressive severity the patient was referred to the Barnes Hospital for further evaluation and treatment on June 10, 1952.

At the time of admission physical examination revealed his temperature to be 38.0°C., pulse 104, respirations 32 and blood pressure 120/80. He appeared well developed and well nourished but was sitting upright, breathing with difficulty. There was no cyanosis. Examination of the eyes and of the fundi was negative. The pharynx was diffusely injected but no exudate was seen. There was no lymph node enlargement. The trachea was in the midline. The veins were not distended. The chest was moderately increased in its anteroposterior diameter; coarse rhonchi and wheezes were heard throughout both lung fields. Resonance was unimpaired. The heart was normal. Abdominal examination was negative as was the rectal examination. There was no edema or clubbing. The neurologic examination was within normal limits.

Laboratory data were as follows: Blood count: red cells, 5,200,000 per cu. mm; hemoglobin, 15 gm; white cells, 13,000; differential: 6 per cent band forms, 71 per cent segmented forms, 21 per cent lymphocytes and 2 per cent monocytes. Urinalysis: specific gravity, 1.028; protein, negative; sugar, negative; sediment, 1 to 2 white blood cells per high-power field. Stool: guaiac negative. Cardiolipin test: negative. Blood chemistry: non-protein nitrogen, 17 mg. per cent; carbon dioxide combining power, 29.6 mEq./L. Sputum smear: numerous

white blood cells with 4 eosinophils per 100 white blood cells. Sputum culture: neisseria and beta-hemolytic streptococci in moderate numbers. Roentgenograms: a chest film revealed changes consistent with pulmonary emphysema and a pleuritic reaction at the left base. Films of the sinuses showed evidence of pan-sinusitis. Electrocardiogram: normal.

The patient was immediately begun on a regimen which included inhalation of an aerosol consisting of a bronchodilator and penicillin, penicillin and streptomycin intramuscularly, aminophyllin intravenously and bed rest. He failed to improve on this therapy. His fever continued and actually increased somewhat. The cough persisted and the patient had considerable difficulty in breathing. In an attempt to control the symptoms more effectively corticotropin was also given, and within two days the patient showed a remarkable response characterized by disappearance of asthma, return of temperature to normal and marked relief of respiratory distress. Repeat x-ray films of the sinuses showed distinct evidence of clearing; nasal polyps, which had been noted shortly after admission, had also disappeared. Skin tests with the usual allergens were negative. Following his rather dramatic improvement the patient was started on postural drainage several times daily and produced large amounts of sputum. Bronchograms which had been done by the patient's own physician in late 1951 were reviewed, and were interpreted as showing cylindrical bronchiectasis in both lower lobes. The patient was discharged from the hospital on June 28, 1952, with instructions to continue postural drainage.

He remained essentially asymptomatic for several months, but was admitted to the hospital for the second time on August 10, 1952, following three days of increasingly severe asthma, associated with a cough productive of moderate to large amounts of white sputum.

Physical examination on this admission revealed the patient's temperature to be 38.0°C. The vital signs were otherwise as before and the physical findings were unchanged. There were rhonchi and numerous wheezes audible over both lung fields.

The laboratory data included a white blood cell count of 14,800, the differential showing 1 per cent basophils, 16 per cent eosinophils, 3 per cent band forms, 60 per cent segmented forms, 18 per cent lymphocytes and 2 per cent monocytes. Vital capacity was 1.8 L. (41 per cent of normal). Sputum smear revealed many pus cells and 5 per cent eosinophils. The non-protein nitrogen was 20 mg. per cent, the carbon dioxide combining power 26.2 mEq./L. A chest roentgenogram revealed pneumonitis in the right middle lobe, emphysema and the pleuritic reaction as previously noted.

The patient was sedated, given aminophyllin, oxytetracycline (terramycin) and an aeorsol of penicillin and a bronchodilator. He gradually improved except for episodes of wheezing during the night which were well controlled by a bronchodilator given sublingually. The patient was discharged from the hospital on August 26, 1952, and was advised to take sulfisoxazole (gantrisin®) in a dose of 1 gm. twice daily. He was also urged to continue postural drainage.

Subsequent to discharge the patient did not do well. He continued to have intermittent episodes of asthma, some of which were quite severe, and on several occasions he required short periods of hospitalization in his home community. Several weeks prior to his third admission he developed a rather severe upper respiratory infection with progressive asthma. On December 19, 1952, he was readmitted.

Physical examination revealed findings similar to those recorded previously. The patient was suffering from severe asthma and many rhonchi, wheezes and groans were heard throughout both lung fields. The laboratory data included a white blood cell count of 16,450 with 4 per cent eosinophils, 75 per cent segmented forms and 21 per cent lymphocytes. The non-protein nitrogen was 15 mg. per cent; chloride, 105 mEq./L., sodium, 141.9 mEq./L. and potassium, 4.1 mEq./L. Sputum culture showed a heavy growth of coagulase-positive hemolytic staphylococcus aureus. A chest roentgenogram revealed the lung fields to be essentially clear. The emphysematous changes previously described were again noted.

The patient failed to respond well to many of the measures previously employed and corticotropin was again given. On this medication he did well and was discharged on January 10, 1953.

Following discharge the patient got along fairly well until ten days prior to his fourth and final admission when he again developed an upper respiratory infection characterized by rhinitis and productive cough. He had no fever or chest pain. Shortly after the onset of the

infection the patient's asthma became very severe and failed to respond to therapy given by his own physician. He was admitted to the Barnes Hospital on February 10, 1953, in status asthmaticus.

Physical examination revealed the temperature to be 37.0°C., pulse 110, respirations 30 and blood pressure 140/80. The patient was acutely ill and extremely orthopneic with very labored, prolonged respirations typically asthmatic in character. There was slight cyanosis. Examination of the chest revealed many coarse rhonchi and inspiratory and expiratory wheezes. The lungs were hyperresonant to percussion. The remainder of the physical examination was similar to that noted previously.

Laboratory data were as follows: red blood cell count, 5.5 million; hemoglobin, 15 gm. per cent; white blood cell count, 18,400; differential; 13 per cent eosinophils, 2 per cent band forms, 67 per cent segmented forms, 17 per cent lymphocytes and 1 per cent monocytes. Urinalysis: negative.

The patient was sedated and given subcutaneous injections of epinephrine without improvement. Oxygen was begun by nasal catheter and the patient received cortisone in a dose of 50 mg. every six hours. He began to improve and the signs in his chest became much less pronounced. On the second hospital day he was sent to the x-ray department for a chest film. While waiting his turn, however, he suddenly developed severe asthmatic breathing and was returned promptly to the ward. While being transferred from the wheel chair to his bed he suddenly stiffened, became cyanotic, and despite all emergency measures he expired on February 11, 1953.

CLINICAL DISCUSSION

DR. CARL V. MOORE: This patient's illness probably dated back to 1936 when at the age of thirty-four he developed symptoms of sinusitis. In 1951 he had the first of a series of upper respiratory infections, some of which were associated with pneumonitis. Beginning in June, 1951, six months after his first attack of pneumonia, the symptoms of asthma appeared. From that time until he expired he had recurrent attacks of asthma associated with respiratory infections. During the course of the illness he developed emphysema, and he also had some evidence of bronchiectasis. Among the points of interest are those relating to the cause of the asthma, the relationship of asthma to emphysema and finally the cause of death. Dr. Seaman, before we begin the general clinical discussion, do you have any comments to make about the roentgenograms?

DR. WILLIAM B. SEAMAN: The first chest film taken in this hospital was obtained in June, 1952, and showed moderate pulmonary emphysema with low diaphragms and an increase in the A-P diameter of the chest. The emphysema was especially marked at the left base. The heart was well within the limits of normal. Several months later films of the sinuses were taken and showed rather extensive clouding of both the maxillary and ethmoid sinuses. A chest film made at the same time showed a little increase in linear streaking in the region of the right middle lobe. Subsequent films in December, 1952, when the patient was in the hospital for the third time, showed no significant change as far as the lung fields were concerned. The only other examination was a bronchogram on December 30, 1952. As noted in the protocol, the right lung was incompletely filled and it was impossible, therefore, to determine whether the patient had bronchiectasis. The bronchi which were visualized appeared to be normal. In the left lung the bronchus to what probably is the middle basilar segment showed slight lobulated dilatation, a change more characteristic of emphysema than of bronchiectasis. The other bronchi on the left side were normal.

DR. C. V. MOORE: Dr. Alexander, this patient was always assumed to have intrinsic asthma. Would you comment on the diagnosis of intrinsic asthma?

DR. HARRY L. ALEXANDER: If an adult has an attack of asthma with typical wheezing and if one examines the sputum of such a patient and finds eosinophils therein, it may be concluded that the patient has asthma. There is no other diagnosis I know which can be applied to that situation. One cannot, however, on the basis of this evidence alone determine whether the patient has so-called extrinsic or allergic asthma or intrinsic or non-allergic asthma. This differentiation, however, is most important, both from the point of prognosis and treatment. (Table 1.) With allergic asthma there is a predisposition to the disease. Many of the patients are born with a tendency to become sensitized, a finding which is usually absent in so-called intrinsic asthma. Allergic asthma is an immunologic phenomenon, a disease involving

an antigen-antibody reaction, and antibody can be demonstrated, either by appropriate skin tests or in the circulating blood. In intrinsic asthma such a demonstration is not possible. Asthma occurring in children and even in young adults is, with rare exceptions, of the allergic type. When asthma comes on after the age of forty or forty-five, the diagnosis of intrinsic asthma should be considered more likely. In this case the patient was forty-seven when he had his first attack, and it would be extremely unusual for a patient to have asthma of this degree, progressing to status asthmaticus, on the basis of hypersensitiveness. One might see such a phenomenon if a drug allergy was responsible but that apparently was not the case here. Another difference between the two forms of asthma concerns the nature of the sputum; although young asthmatics produce mucoid sputum, it is not the tough, thick, gelatinous and inspissated type of secretion that one sees in older individuals with intrinsic asthma. Extrinsic asthma, if present long enough, may lead to emphysema and bronchitis, but in intrinsic asthma cor pulmonale and even polyarteritis may complicate the disease. Furthermore, emphysema develops more quickly. The prognosis in extrinsic asthma is relatively good because therapeutic methods are efficacious; either the sensitizing agent can be removed or the patient may be desensitized to it. In intrinsic asthma treatment is only symptomatic. Of great importance is the fact that patients with allergic asthma rarely die of the disease, provided the physician refrains from doing something detrimental to them such as administering serum, performing an inappropriate skin test or prescribing a drug to which the patient is sensitive. There is an old French proverb to the effect that "asthma is the brevet of long life." We had the opportunity in this clinic in 1928 of having reported the twenty-eighth, twenty-ninth and thirtieth autopsied cases of bronchial asthma in the world literature. This fact is significant when one realizes that asthma has been known since the year 300 A.D. Conversely, patients with intrinsic asthma may indeed succumb to their disease. Thus the mortality statistics are of the order of 5 per cent. Many of the patients do not die in an asthmatic attack, but they may die of extreme emphysema, cor pulmonale or polyarteritis. It is my belief that intrinsic asthma is a relatively new disease, one which has been recognized only in the past thirty years. Perhaps it is similar to the other so-called collagen diseases which now seem so common and which were so unusual twenty or thirty years ago.

TABLE 1

	Allergic Asthma	Non-allergic Asthma
Predisposition (family—past history of allergy,)	Present	Usually absent
Sensitizing antibodies (circulating, positive skin reactions)	Present	Absent
Age of onset	Earlier years	Middle age and after
Bronchial mucus	Present	Excessive
Specific treatment	Available	Not available
Complications	Bronchial emphysema	Bronchitis, emphysema, cor pulmonale, polyarteritis
Prognosis	Good	Uncertain
Mortality	Unusual	Over 5 per cent

DR. C. V. MOORE: In the case we are discussing what do you believe the role of infection was in the production of asthma?

DR. ALEXANDER: There are distinguished authorities in this field who believe that asthma following pulmonary infection results from bacterial allergy. This hypothesis seems well taken because infection so obviously initiates the episodes. The inference, however, that hypersensitiveness to bacterial products is responsible is difficult to prove. Infection is apt not only to initiate an attack but also to make it worse. One reason for the latter fact is that in the presence of infection the patients have not only thick, tenacious mucous in the bronchi and bronchioles but also pus and inflammatory changes as well. Thus when one is able to treat the infection successfully, the patient may be benefited sufficiently to emerge from the attack.

DR. C. V. MOORE: Is the evidence relating infection as a trigger mechanism so clear-cut that you would recommend lobectomy for a patient with bronchiectasis, confined to one lobe, where asthma had supervened?

DR. ALEXANDER: No. I do not recall ever having seen a patient with bronchiectasis confined to one lobe and with no bronchitis elsewhere. Perhaps such a situation occurs but it must be extremely unusual.

DR. C. V. MOORE: Dr. Bukantz, Dr. Alexander and I were discussing this case just prior

to the conference. He voiced strong objection to the way in which the sputum eosinophilia was expressed. Since it is your assignment each year to discuss this subject in the course in Laboratory Diagnosis, may I ask if you likewise object to the reporting of sputum eosinophils in percentage? If so, how should the results be given?

DR. SAMUEL C. BUKANTZ: It would be preferable for Dr. Alexander to answer that question, Dr. Moore, since he has been particularly critical of the usual method of estimating eosinophils in sputum. I can say that I think reporting eosinophils in the sputum in terms of percentage is not satisfactory.

DR. ALEXANDER: I have discussed this subject frequently but at the risk of being tiresome I will comment on it again. It is extremely difficult and probably impossible to do an accurate differential count on sputum. Because of the viscosity of the sputum one cannot obtain a representative sample; thus if one examines a sputum smear, he will be struck by the tremendous variation in cell pattern from one field to another. In practice either there are great numbers of eosiniphils present or there are essentially none. There should be no difficulty in finding eosinophils in myriads if sputum is processed properly. This procedure is extremely important because it enables the clinician to differentiate between bronchial asthma, either with or without infection, from infection alone.

DR. C. V. MOORE: In other words you believe it much more desirable to report eosinophils in the sputum as being many or very few without attempting to quantitate them in terms of per cent?

DR. ALEXANDER: That is correct.

DR. BUKANTZ: There was a case in this hospital some years ago in which the absence of eosinophils from the sputum of an apparent asthmatic caused some concern. The patient died after a brief illness and at postmortem examination many eosinophils were found in the secretions within the smaller bronchioles. It is thus possible that eosinophils may not be identified in the sputum, particularly if an adequate specimen is not available.

DR. ALEXANDER: I remember the case to which you refer. It is true that in a rare case of bronchial asthma sputum eosinophils are not demonstrable. On the other hand, in your wide experience how many cases of bronchial asthma have you seen in which sputum properly prepared and examined did not show eosinophils?

DR. BUKANTZ: To this day I have seen none, because I don't make the diagnosis of bronchial asthma unless eosinophils are found in the sputum.

DR. C. V. MOORE: Are there any other comments?

DR. BUKANTZ: Dr. Moore, it is appropriate to the question which you asked Dr. Alexander that Dr. Alfred Goldman has under observation at present a very interesting case which I have been privileged to see with him on several occasions. In this instance localization of bronchiectasis to one area of the lung was demonstrated and its possible relation to asthma of the intrinsic type was considered. In this patient operation for bronchiectasis was performed.

DR. C. V. MOORE: Dr. Goldman, will you tell us about your patient?

DR. GOLDMAN: The patient had not only bronchiectasis but also atelectasis of the right upper lobe which probably had been present for many years. As a result there was marked distortion of the middle and lower lobes on the right; as a matter of fact the middle lobe was pulled almost to the apex of the lung. Presumably these structural changes resulted from an old tuberculous process. There was also a slight amount of atelectasis and bronchiectasis of the left upper lobe as well, but no evidence of active tuberculosis, despite very careful studies. Six or seven months ago the patient developed what appeared to be typical bronchial asthma; her sputum contained eosinophils in large numbers, and there were also eosinophils in the peripheral blood. Because it was thought that at least some of her symptoms were due to distortion of the middle and lower lobes resulting from atelectasis, lobectomy was performed. For two months after removal of the right upper lobe the patient was free of asthma. Neither the sputum nor the peripheral blood showed eosinophils. A few days ago, shortly after the patient returned to her home, she had an attack of asthma which occurred during house-cleaning while there was much dust in the air. I suppose this patient could be considered to have intrinsic asthma.

DR. BUKANTZ: When I saw the patient I thought that most of her respiratory symptoms were due to bronchial asthma secondary to the chronic localized infection in the right upper lobe.

DR. GOLDMAN: This consideration also lent support to the decision to have the lobectomy done.

DR. BUKANTZ: The subject has been discussed in a recent article by Overholt, Walker and Woods.[1] A more moderate view of the surgical attitude was expressed in an editorial in a recent issue of the Journal of Allergy.[2]

DR. C. V. MOORE: Dr. Goldman, in the patient we are discussing today it is of interest to attempt to determine whether emphysema existed prior to the onset of his first respiratory symptoms early in 1951. The chest roentgenograms made in this hospital in June, 1952, showed evidence of emphysema. Do you think it possible that the degree of emphysema noted could have developed in eighteen months, or do you think the patient probably had emphysema prior to the present illness?

DR. GOLDMAN: In view of the fact that he was well prior to 1951, and considering the rather severe nature of his illness, I believe it is certainly possible that he developed emphysema in the two years prior to his death.

DR. C. V. MOORE: Dr. Schroeder, do you think this patient had cor pulmonale? Despite the emphysema and bronchial asthma the diagnosis of cor pulmonale was not made during his lifetime. An electrocardiogram done in the summer of 1952 was read as normal.

DR. HENRY A. SCHROEDER: It is difficult to say clinically exactly when the state of cor pulmonale begins. This man did not have any signs of right-sided heart failure but he undoubtedly had pulmonary hypertension, and if he had pulmonary hypertension for a prolonged period there is reason to suspect that hypertrophy of the right ventricle would develop. There are three factors which influence pressure in the pulmonary circuit. One is structural. That is to say, changes in the alveoli produce increased resistance to capillary flow; if fibrosis occurs the obstruction is particularly severe. The second factor is probably an actual spastic element, i.e., spasticity of the arteries and arterioles in the pulmonary circuit. Thus it has been shown experimentally that anoxia itself will cause pulmonary vasoconstriction in experimental animals, and it is known that in some patients pulmonary hypertension can be partially relieved by the use of appropriate vasodilators. Third, arteriosclerotic changes in the vessels enhance pressure in the pulmonary circuit. In the present case, right ventricular hypertrophy will probably be found.

DR. C. V. MOORE: Do you agree with Dr. Schroeder, Dr. Bukantz?

DR. BUKANTZ: For the most part, yes, but I take some exception to the importance of structural changes in the pathogenesis of pulmonary hypertension. These seem much less important than the functional changes. I agree that it is probable that the patient will have evidence of cor pulmonale as judged by the ultimate criterion, namely, increased thickness of the right ventricular wall. Nonetheless, evidence that cor pulmonale played a significant role clinically is absent.

DR. C. V. MOORE: During the patient's second admission, at a time when he was relatively free from asthma, his vital capacity was 1.8 L., a value approximately 40 per cent of normal. Presumably, therefore, at the time he died he certainly had no more pulmonary reserve than that and probably less. The question of oxygen therapy comes up, Dr. Flance, in this regard. It is generally stated in textbooks that when patients have bronchial asthma, particularly with status asthmaticus, oxygen therapy is indicated. Yet recent studies[3,4] suggest that patients with severe emphysema, if given oxygen therapy, may do badly because of the accumulation of carbon dioxide. How do you handle this difficult problem in practice?

DR. I. JEROME FLANCE: It is indeed a difficult problem, Dr. Moore, and treatment must be individualized. To some extent, the degree of anoxia present is important. Also, the presence or absence of respiratory acidosis, compensated or uncompensated, must be considered. We have not hesitated to use oxygen in small amounts in the treatment of anoxic patients, even though the carbon dioxide combining power is elevated, but such patients, of course, must be observed with extreme care. One can employ the Drinker respirator under these circumstances, although we have not had much success with it because patients have great difficulty in adjusting their breathing to the

[1] OVERHOLT, R. H., WALKER, J. H. and WOODS, F. M. Hidden or unsuspected bronchiectasis in the asthmatic patient. *J. A. M. A.*, 150: 438, 1952.

[2] Editorial. Asthma associated with bronchiectasis. *J. Allergy*, 24: 187, 1953.

[3] SCHILLER, I. W., BEALE, H. D., FRANKLIN, W., LOWELL, F. C. and HALPERIN, M. H. The potential danger of oxygen therapy in severe bronchial asthma. *J. Allergy*, 22: 423, 1951.

[4] CALLAWAY, J. J. and MCKUSICK, V. A. Carbon dioxide intoxication in emphysema: emergency treatment by artificial respiration. *New England J. Med.*, 249: 9, 1951.

respirator cycle. Respirator treatment may be particularly important in combatting carbon dioxide narcosis in emphysematous patients.

DR. C. V. MOORE: Dr. Alexander, do you have any additional comments to make?

DR. ALEXANDER: Most of the recommendations in the literature in regard to the use of oxygen in patients with asthma antedate the more recent observations, to which you have alluded, concerning the dangers of prolonged oxygen therapy in severe emphysema.

DR. BUKANTZ: I have been impressed by the fact that many patients with status asthmaticus do not exhibit much cyanosis. In other words, despite the presence of severe asthma, there may not be enough anoxia to produce cyanosis. In such a case it is doubtless wise to avoid the use of oxygen, and to rely on agents directed against the disease *per se*.

DR. C. V. MOORE: Dr. Glaser, several years ago Dr. Wilson and Dr. Alexander published a paper concerned with the relationship of eosinophilia to bronchial asthma and its significance in terms of the occurrence of polyarteritis nodosa.[5] This patient had a consistently elevated eosinophil count, with levels often of the order of 15 per cent. Do you believe that polyarteritis should be considered seriously?

DR. ROBERT J. GLASER: The presence of that degree of eosinophilia associated with asthma should bring to mind the possibility of polyarteritis nodosa, although in general the patients whom Dr. Alexander and Dr. Wilson described[5] had eosinophilia of much greater magnitude, averaging about 50 per cent. The association of polyarteritis nodosa and asthma, emphasized somewhat earlier by Rackemann and Greene,[6] must always be kept in mind, but in my opinion unless the eosinophilia is of a greater degree polyarteritis is probably not too likely.

DR. C. V. MOORE: This patient had a normal blood pressure, and no evidence of renal or hepatic dysfunction. Do you think these facts enable one to disregard the diagnosis of polyarteritis nodosa, Dr. Wood.

DR. W. BARRY WOOD, JR.: Not completely.

DR. C. V. MOORE: Do you have any comments on this point, Dr. Alexander?

[5] WILSON, K. S. and ALEXANDER, H. L. The relation of periarteritis nodosa to bronchial asthma and other forms of human hypersensitiveness. *J. Lab. & Clin. Med.*, 30: 195, 1945.

[6] RACKEMANN, F. M. and GREENE, J. E. Periarteritis nodosa and asthma. *Tr. A. Am. Physicians*, 5: 112, 1939.

DR. ALEXANDER: In my experience it is somewhat unusual for an adult with uncomplicated bronchial asthma to have 16 per cent eosinophils in the peripheral blood. It occurs from time to time but it falls within the range in which polyarteritis nodosa occurs. As Dr. Glaser pointed out, however, eosinophilia in our series was more pronounced. It is important to emphasize that some of the patients had neither hypertension nor evidence of renal disease.

DR. C. V. MOORE: You would agree, then, that the possibility of polyarteritis nodosa must be entertained.

DR. ALEXANDER: Yes. Had the patient lived longer a muscle biopsy would have been justified.

DR. C. V. MOORE: Finally, let us consider the mechanism of the sudden death in this patient. The house officer was at the patient's side when he died, and observed that the heart continued to beat for at least four minutes after respiration had ceased. All attempts, however, to revive the patient were unsuccessful. Dr. Bukantz, you were interested in the nature of this terminal event. Would you comment on the circumstances which occurred here?

DR. BUKANTZ: I might say in passing that I saw this patient on two occasions and was very much intrigued by his resistance to therapy and by the question of the etiologic role of infection in perpetuating his asthma. It was also of interest that the patient was a very dependent person. His wife hovered over him like a hen over a brood during each of his hospital admissions. We were distressed by our difficulty in establishing a satisfactory therapeutic program because he lived at some distance from St. Louis. I believe that had the geographic situation been more favorable we might have been much more helpful to him. On his last admission the patient entered in status asthmaticus, was given cortisone and apparently was improving. On the second day he was, therefore, sent to the radiology department for a chest roentgenogram. Shortly after arrival there he appeared to develop a recurrence of his symptoms and he was rushed back to the ward. As described in the protocol, while he was being transferred from the wheel chair to the bed, he died suddenly. Earlier in the discussion, Dr. Alexander alluded to the fact that some patients with asthma die as a result of medical intervention, that is, because they are given a drug to which they are sensitive. I was interested here in the

possible role of penicillin anaphylaxis. This patient had been given penicillin although we are not certain how soon before the terminal episode the injection was given. Both on the temperature graph as well as in the nurses notes it was indicated that 600,000 units of crystalline penicillin had been administered before the patient was sent to the x-ray department. As near as can be determined, he probably had had the injection forty to fifty minutes before the terminal episode. That interval seems long for anaphylactic shock, but it is of interest that anaphylactic shock may occur with some delay. Recently in conjunction with some laboratory studies the question of delayed anaphylaxis arose and I took occasion to discuss the problem with Dr. Jules Freund. In his experienced opinion delayed anaphylaxis may occur, at least in experimental animals. On the other hand in man most of the cases of anaphylaxis due to penicillin have come on suddenly. The point cannot be settled definitively, but it is conceivable that penicillin sensitivity was responsible for this man's death. Caution should certainly be exercised in administering repeated injections of penicillin to asthmatics, for the number of anaphylactic deaths due to penicillin is increasing alarmingly.

DR. ALBERT I. MENDELOFF: If this patient had not been an asthmatic, one certainly would have suspected pulmonary embolism.

DR. C. V. MOORE: You are quite correct, Dr. Mendeloff, but because we have discussed pulmonary embolism, cardiac arrthymias and other common causes of death often at these conferences, I did not introduce them for consideration. I would like to ask Dr. Goldman one more question. In the protocol it is stated that following therapy with ACTH, nasal polyps disappeared. Have you seen this happen?

DR. GOLDMAN: Yes, I have.

DR. C. V. MOORE: In summary then we believe this patient had intrinsic asthma, bronchiectasis and emphysema, and possibly cor pulmonale and polyarteritis nodosa. Whether the sudden death was due to an anaphylactic reaction to penicillin has been considered.

Clinical Diagnoses: Bronchiectasis, emphysema, bronchial asthma, ? cor pulmonale, ? polyarteritis nodosa, ? anaphylaxis due to penicillin.

PATHOLOGIC DISCUSSION

DR. EMIL FREI: On opening the thorax the lungs were found to be markedly voluminous, pale gray, and to fill the thoracic cavity. On the cut surfaces the parenchyma was dry and emphysematous. The tracheobronchial tree was filled with very thick, tenacious mucus. The bronchi of the basilar segments bilaterally were found to be cylindrically dilated to a slight degree and could be opened to within 2 or 3 mm. of the pleura. The heart was enlarged, weighing 400 gm.; the right ventricle was particularly thickened. The remaining viscera were not remarkably altered. There was moderate passive congestion of the liver, spleen and kidneys, and petechiae were scattered throughout the gastrointestinal tract. The adrenals were normal in size and appearance. The brain contained no significant lesions.

DR. ROBERT A. MOORE: As may be judged from the paucity of findings described grossly, pathologists have very little to contribute in a discussion of asthma. The emphysematous lungs, the thick mucus filling the tracheobronchial tree, and the slight cardiac hypertrophy, predominantly on the right side of the heart, are typical. In this case, the microscopic changes are also classical. Figure 1 is an illustration of a section of the wall of a large bronchus with the lumen on the left. The bronchus is completely filled by thick, homogeneous, stringy basophilic material with the appearance typical of mucus in asthma. Throughout this mucus and in the connective tissue of the bronchus there are scattered cells, most of which are eosinophilic leukocytes. The epithelial layer itself is of columnar cells that show no evidence of metaplasia. Beneath the epithelium there is an acellular, acidophilic, homogeneous basement membrane which is three to five times as thick as normally. The underlying dense connective tissue is heavily infiltrated, almost exclusively by eosinophilic leukocytes. Beyond the bronchial cartilage there can be seen mucous glands which are hypertrophied; they are shown in greater detail in Figure 2. In the illustration the bronchial lumen lies above the edge of the photograph. The tubular structure which extends downward in the center is the duct of the mucous gland. The surrounding acini are tremendously hypertrophied and packed with mucus, so that both the acini and the duct are many times normal size. Figure 3 shows the fifth typical change in the wall of the bronchus, namely, a greatly thickened and hypertrophied muscular layer, approximately two or three times the normal for a bronchus

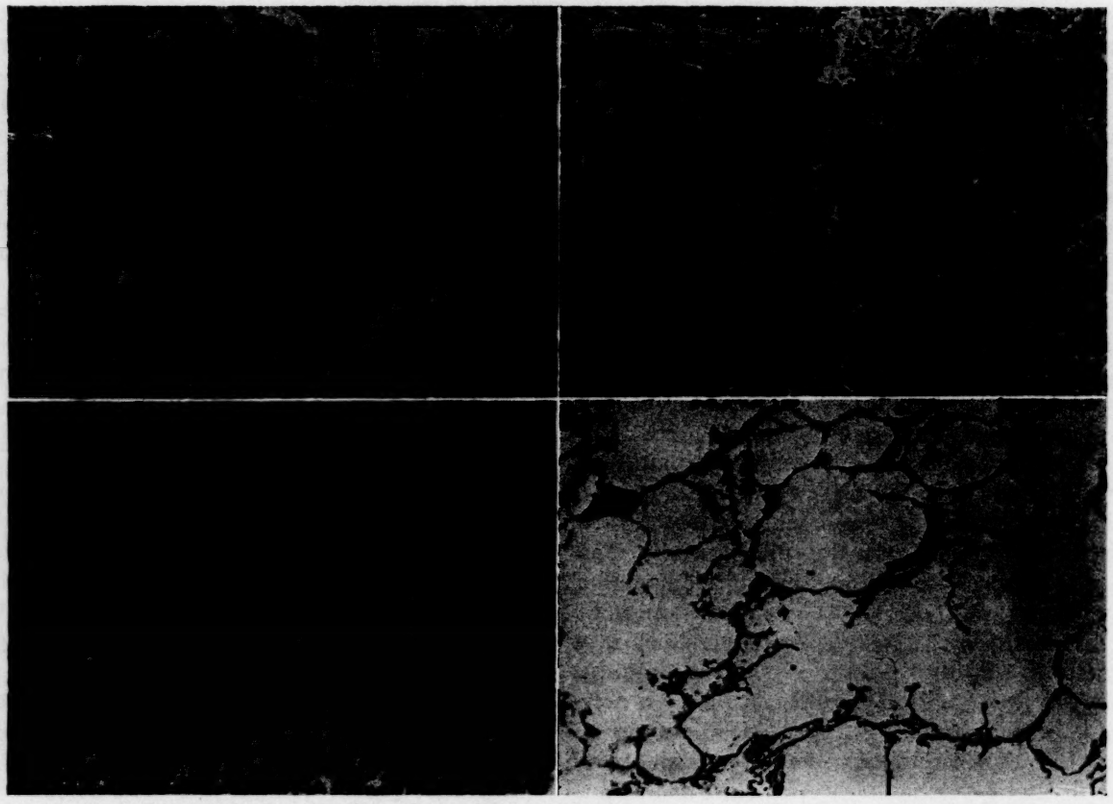


FIG. 1. A segment of the wall of a major bronchus in bronchial asthma, showing thick mucus in the lumen on the left of the photograph, a thickened basement membrane, cellular infiltration in the submucosa and increased mucous glands. The cells infiltrating the submucosa are largely eosinophilic leukocytes. FIG. 2. Hypertrophy and distention of the mucous glands of the wall of the bronchus in bronchial asthma. FIG. 3. Hypertrophy of the muscular layers in the wall of a bronchus in bronchial asthma. FIG. 4. Emphysema of the lungs.

of this size. The other findings noted in Figure 1 are also illustrated here.

These three figures illustrate the histologic and anatomic findings on which most pathologists agree that an objective anatomic diagnosis of asthma can be made with reasonable certainty. In recapitulation these are: (1) A large amount of thick mucus in the lumen of the bronchi; (2) hyaline thickening of the basement membrane of the bronchial epithelium; (3) hypertrophy of the bronchial muscle; (4) distention of the bronchial mucous glands and their ducts and (5) the presence of numerous eosinophilic leukocytes among the inflammatory cells in the bronchial wall. The final illustration (Fig. 4) is simply an over-all view of a section of the lung showing the microscopic appearance of advanced emphysema. The greatly dilated air sacs and the bulbous ends of septal walls are characteristic. The arterioles throughout the pulmonary tissue showed slight thickening indicative of pulmonary arteriolar disease, but the major vessels did not show any significant degree of arteriosclerosis. There was no evidence in the lungs or any other organ of the lesions of polyarteritis nodosa, nor were evidences of any other significant pathologic process present. The lesions observed are simply those that were expected in confirmation of the clinical diagnosis of asthma.

DR. ALEXANDER: The large amount of extremely viscid mucus in the tracheobronchial tree in cases such as this is always impressive. Is it the belief of pathologists that this is normal mucus from normal glands merely present in an excessive amount, or is there any indication that this secretion represents an abnormal product of abnormal glands?

DR. R. A. MOORE: Certainly this material does not have the appearance of ordinary mucus. It is of a much greater viscosity, and it has different staining characteristics, although its

greatly increased basophilia may be due at least in part to its viscous state. Dr. Sidney Farber has studied the abnormal mucus in infants with cystic fibrosis of the pancreas, and has shown that it is a definitely abnormal substance. Such studies might be profitably pursued in connection with the mucus of asthma, but have not been reported as yet to my knowledge.

DR. ALEXANDER: Dr. Bukantz has been especially interested in the problem of the nature of the secretions in asthma. Perhaps he would comment on his observations.

DR. BUKANTZ: I think that at least part of the answer in the management of the intractable asthmatic lies in a better interpretation and understanding of the mucus substrates involved. To date, we have only applied to asthmatic sputum what other investigators are doing in the analysis of non-bronchial mucins. The extremely gelatinous material obtained from an asthmatic was subjected to hydrolysis and chromatographic analysis. We have demonstrated that it is extremely rich in protein-containing or polypeptide material, but there is nothing unusual in the distribution of amino acids. Our chief interest stems from the fact that there is increasing evidence that hydrolytic and proteolytic enzymes and detergents, and particularly the non-ionic type, will alter the viscosity of thick secretions. Some of these agents have already been introduced as aerosols in the treatment of patients with asthma.[7,8] It remains for future investigations to disclose which of these, singly or in combination, will be most effective.

Final Anatomic Diagnoses: Advanced emphysema; tenaceous mucus in the bronchi; bronchiectasis in the lower lobes of the lungs; hypertrophy and dilatation of the heart, predominantly of the right ventricle.

Acknowledgment: Illustrations were made by the Department of Illustration, Washington University School of Medicine.

[7] LIMBER, C. R., REISER, H. G., ROETTIG, L. C. and CURTIS, G. M. Enzymatic lysis of respiratory secretions by aerosol trypsin. *J. A. M. A.*, 149: 816, 1952.

[8] MILLER, J. B. and BOYER, E. H. A nontoxic detergent for aerosol use in dissolving viscid bronchopulmonary sections. *J. Pediat.*, 40: 767, 1952.

Case Reports

Renal Hyperchloremic Acidosis*

Familial Occurrence of Nephrocalcinosis with Hyperchloremia and Low Serum Bicarbonate

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A specific syndrome was separated from the complex of renal tubular disorders by Butler, Wilson and Farber[1] in 1936 and Albright et al.[2] in 1940. The many titles under which this syndrome has been described are presented in Table I. Case descriptions appear in these and other articles.[17–19] The clinical syndrome includes several essential features which are classified in Table II.

TABLE I
TERMS USED TO DESCRIBE RENAL ACIDOSIS

1. Nephrocalcinosis infantum with hyperchloremic acidosis[3]
2. Nephrocalcinosis with rickets and dwarfism[2]
3. Concomitance of chronic acidosis with late rickets[4]
4. Idiopathic renal acidosis[5]
5. Persistent acidosis[6]
6. Lightwood's syndrome[7,8]
7. Renal acidosis resulting from tubular insufficiency without glomerular insufficiency[9]
8. Butler-Albright syndrome[10]
9. Nephrocalcinosis with chronic tetany[11]
10. Renal tubular acidosis with osteomalacia[12]
11. Renal hyperchloremic acidosis[13]
12. Hyperchloremic acidosis and nephrocalcinosis[14]
13. Distal tubular dysfunction with renal calcification[15]
14. Chronic acidosis of renal origin[16]

Despite the excellent clinical studies and vigorous experimentation which have been stimulated by the broad physiologic implications of this disease, several fundamental questions have been left unanswered: What is the etiology of this disorder? What is its pathogenesis? Which of the manifestations of renal impairment are primary and which are secondary to the calcification and infection so often present when the advanced stage is clinically recognized?

Two patients with this syndrome afforded the opportunity to approach some of these problems. The present report is concerned with the clinical features and with a family study which is the first clear evidence that this disease may exist on a familial basis. The term "familial renal acidosis" would be applicable to the family of Case I.

CASE REPORTS

CASE I. A twenty-eight year old white man entered the hospital in August, 1951, complaining of pain in the right flank. He had had scarlet fever and pertussis as a child and pneumonia (morbidity six months) at age twelve. One episode of red urine was noted at age 20. He had had six subsequent years of satisfactory military service in Africa, Germany and Alaska. During 1950 there was a heavy alcohol intake and he had one gonorrheal infection. In November, 1950, he reported to a dispensary with right costovertebral angle pain of sudden onset, dysuria and frequency. Laboratory data confirmed the presence of renal infection, with hyposthenuria and an alkaline urine. In December, 1950, he had a recurrence of back pain and dysuria. Examination revealed tenderness in the right costovertebral angle and the right lower abdominal quadrant, and a right inguinal hernia. Cystoscopy revealed cystitis secondary to renal infection. The x-ray of the abdomen was read as showing "countless minute calcifications in both renal pelves." Urinary specific gravities ranged from 1.006 to 1.009. A urine culture was positive for Pseudo-

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monas aeruginosa. PSP excretion totaled 50 per cent in two hours. Serum calcium was reported as 10.5 and 17.0 mg. per cent on two occasions. The pyuria cleared following treatment with antibiotics. Diagnoses of "pyelitis" and "hyperparathyroidism" were made and surgery was proposed.

In February, 1951, at an Army station hospital the x-ray and physical examination were unchanged but the observation of calcified mesenteric nodes prompted a roentgenologic diagnosis of "tuberculous lesions with calcification." The urine was alkaline, with a specific gravity of 1.010 and a positive Sulkowitch test. The serum calcium levels were 10.9, 11.1, 11.2, 12.5, 10.8, 11.0 and 10.3 mg. per cent. Alkaline phosphatase determinations were 3.6 and 1.6 Bodansky units. CO_2 combining power was 18 and 22 mEq./L., the serum Cl was 120 mEq./L., and PSP excretion was 49 per cent in two hours. The diagnosis of hyperparathyroidism was not substantiated and the patient was discharged.

In July, 1951, he was readmitted with severe right flank pain and was again treated for pyelonephritis. The serum calcium was 13.5 mg.; inorganic phosphorus was 3.5 mg.; and blood urea nitrogen was 16.5 mg. per cent.

A repetition of this episode in August, 1951, prompted transfer of the patient to Walter Reed Army Medical Center. The past history and physical examination were unchanged except for the additional information that the patient habitually drank a quart or more of milk per day. Slit lamp examination of the eye and roentgenographic search of the orbits and soft tissues failed to reveal any local calcification other than the previously noted mesenteric nodes. There was notable absence of demineralization of bones, which may be directly related to the history of milk ingestion. However, a careful family history on this patient revealed the familial pattern which is presented in Figure 1. Although this family lived in a poorly accessible area, an attempt was made personally to survey all the members. Whenever permitted, blood was drawn under oil, centrifuged and returned

TABLE II

CLASSIFICATION OF CLINICAL FEATURES OF RENAL ACIDOSIS

	Case I	Case II
1. Defective urinary acidification manifested by:		
a. Alkaline or sub-acid pH	6.5–7.5	7.0–7.5
b. Sub-normal titratable acidity	50% of control	Slight decrease
c. Low ammonia output	50% of control	25% of control
d. Excessive Na, K and Ca excretion which may lead to hypokalemia or tetany	Yes	Yes
2. Systemic acidosis manifested by:		
a. Low blood pH	7.28–7.33	7.31
b. Hyperchloremia	110–115 mEq./L.	110–121 mEq./L.
c. Low CO_2 content	13.9–20.5 mEq./L.	17.3–20.2 mEq./L.
3. Defective end organ response to antidiuretic hormone manifested by:		
a. Polyuria	3.45 l/day	No
b. Polydipsia	No	No
c. Hyposthenuria	Maximum specific gravity 1.010	Maximum 1.010
d. Dehydration	Yes	Yes
e. Impaired response to pitressin injection	Yes	Yes
4. Nephrocalcinosis and/or nephrolithiasis manifested by:		
a. Ureteral colic	Yes	Yes
b. Secondary pyelonephritis	Yes	Yes
c. Characteristic x-ray findings of granular calcium deposition predominantly in the pyramids	Figure 2	Figure 5
5. Bone disease manifested by:		
a. Low phosphorus, rickets, and stunted growth in children	No	No
b. Pathologic fractures	No	No
c. Demineralization in adults	No	No
6. Progressive impairment of renal function	Slight	Slight

to our laboratory under refrigeration. Urine pH was measured and sediment examined twelve hours after voiding. The results are plotted on Figure 1. While the data suggest hyperchloremia in other members of the family, we hesitate to depend on a single laboratory determination. Emphasis is placed, therefore, only upon those members of the family with radiologic confirmation of nephrocalcinosis. Such calcification has been found in the patient (Fig. 2), his brother (Fig. 3) and his son. (Fig. 4.) Thus three of the four x-rays taken were positive.

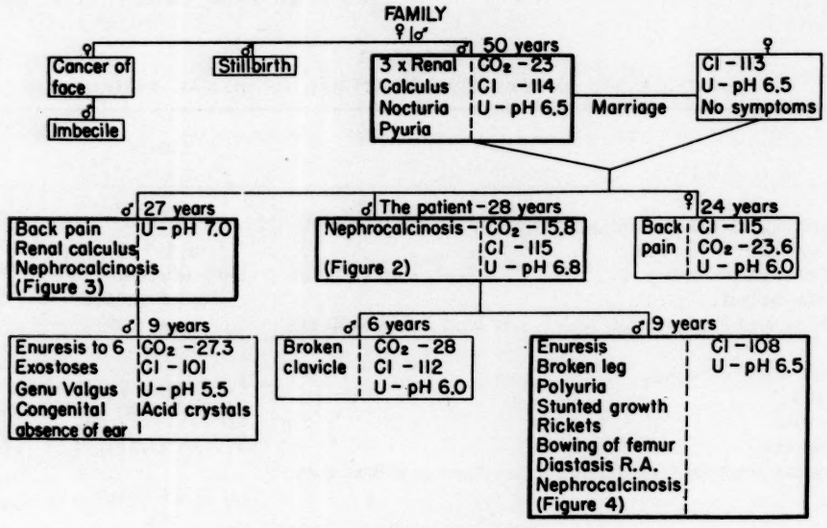

FIG. 1. The family history of Case 1.

The patient's serum calcium, inorganic phosphorus and alkaline phosphatase have remained normal over a one-year period of observation. The CO_2 content has ranged from 15.8 to 20.5 mEq./L. in the untreated state and from 23.1 to 25.8 mEq./L. when treated with 8.5 gm. sodium bicarbonate per day. Blood chlorides were 110 to 115 mEq./L. when untreated and have progressively decreased to 102 mEq./L. under treatment. Serum Na and K have not shown significant variations. There has been no azotemia. Urine pH has ranged from 6.5 to 7.5 (mean 6.95). Specific gravity has ranged from 1.003 to 1.010 during dehydration tests and after pitressin injection. Pyuria has been persistent, PSP excretion has changed from 46 per cent in one hour to 80 per cent one hour after treatment. Urea clearance has changed from 73 to 88 per cent of the calculated normal. Endogenous creatinine clearance was 84 ml./min. At present the addition of sodium bicarbonate has apparently corrected his chemical abnormalities. He has been discharged from the hospital and has returned to work. His only symptoms are polyuria and occasional dysuria from the passage of gravel.

The patient's *brother* who is twenty-seven years old had had seven hospitalizations in 1944, one in 1945, six in 1948 and two in 1949–50. He was discharged from hospitals in 1944 with diagnoses of psychoneurosis, anxiety, hysteria and borderline mental deficiency. In 1945 he sustained a fractured mandible. Healing was uneventful. In 1948 a typical case of infectious hepatitis developed. The discovery of asymptomatic pyuria in a routine urinalysis led to investigation of the patient's genitourinary tract and a final diagnosis of "nephrolithiasis and nephrocalcinosis" was made. An intravenous pyelogram showed dye excretion and bilateral hydronephrosis. The serum calcium was 10.8 and 11 mg. and inorganic phosphorus determinations were 4.1 and 6.1 mg./100 ml. of serum. The classic x-ray of nephrocalcinosis showing the pyramids of a kidney outlined with dye is seen in Figure 3.

This man also has no evidence of bone disease. During a recent interview he related that he drank at least 1 quart of milk per day from early childhood. This intake was reduced during military service but since discharge he has been drinking 3 quarts per day. He passes gravel at frequent intervals and has required several catheterizations for obstruction during the past three months.

The patient's *son*, age nine, has shown poor school performance (failed the first grade). He has frequent colds and has been hospitalized three times with "pneumonia." Since earliest childhood he has had polyuria, polydipsia and continued enuresis. He was considered to have rickets as a newborn and fractured his femur at age four. Healing time was not noted. On examination there was definite retardation of growth (he is the same height as his six year old brother), bowing of both femurs, flaring of costal margins and severe diastasis of the rectus abdominis muscle. An abdominal x-ray demonstrated classic nephrocalcinosis and rachitic changes in the femur, as seen in Figure 4. The patient's other son, age six, appears completely normal and has negative x-ray findings.

The patient's *father* who is fifty years old has chronic bronchial asthma. He has had burning on urination for twenty years. In 1936 he experienced six to eight bouts of right lower quadrant pain radiating into his testicles. In 1941 he was examined for left lower abdominal pain. A diagnosis of "renal calculus" was made, and he later passed a stone. In 1946 he had right lower quadrant pain diagnosed as "renal

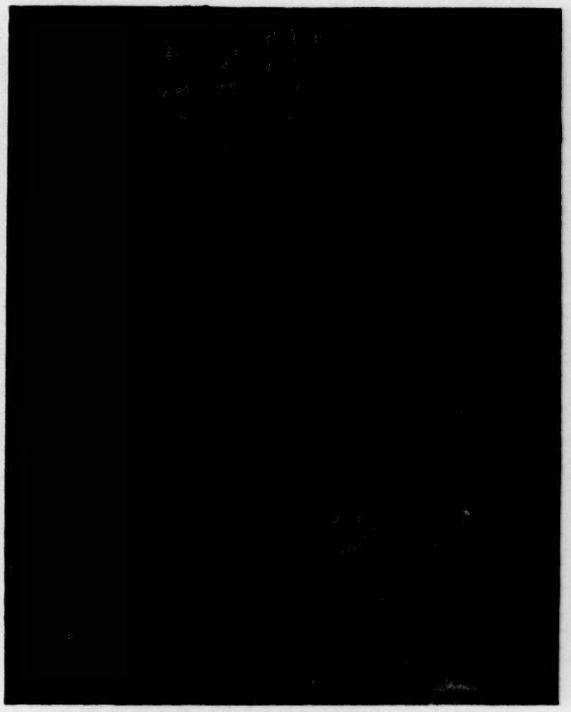

FIG. 2. Case 1. X-ray of the abdomen showing discrete calcifications in the renal parenchyma. The lesions are most marked along the renal pyramids.

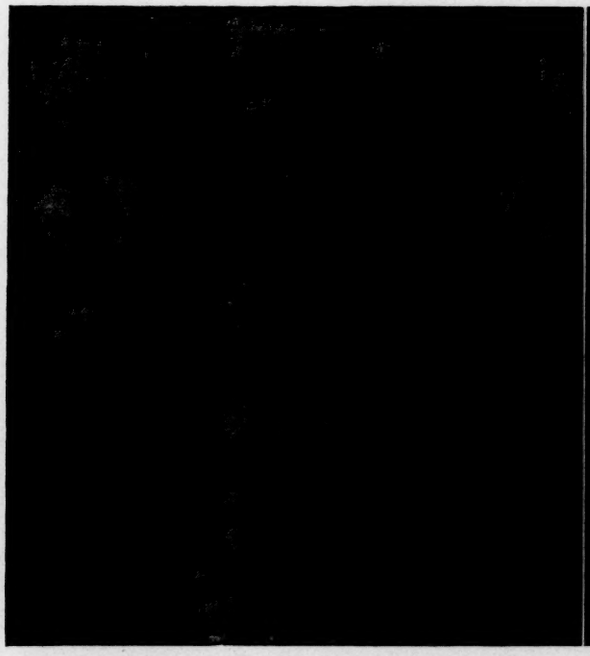

FIG. 3. Brother of patient in Case 1. X-ray of the abdomen following the injection of diodrast. Discrete calcifications are seen in the renal parenchyma and the dye outlines bilateral hydronephrosis and hydroureter.

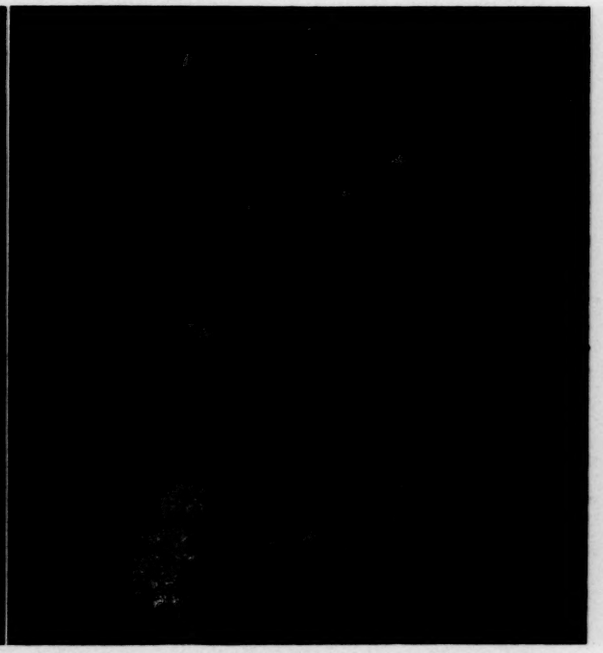

FIG. 4. Son of patient in Case 1. X-ray of the abdomen showing early nephrocalcinosis. The right femur shows evidence of the fracture at age four. Childhood rickets was also present.

colic." (Both episodes have been verified from physician's records.) He has had nocturia once or twice for six years, and one episode of hematuria. His left arm was fractured in 1936 and right shoulder in 1940, both following trauma. Healing was uneventful. Efforts to obtain further studies of this individual have been unsuccessful because of his refusal to cooperate.

The patient's *nephew* (son of the affected brother), age nine, gave a history of polyuria and enuresis to age six. On examination in 1951 he had multiple exostoses, principally on the tibia, radius and ulna, genu valgum and congenital absence of one ear. He had a blood CO_2 of 27.3 mEq./L., serum chloride of 101 mEq./L., and a urine pH of 5.5. When seen one year later he complained of pains and weakness in the leg muscles aggravated by walking. He also experienced a general weakness on arising early in the morning. His legal custody had been awarded to the grandfather who refused permission for either an x-ray or additional chemistry.

CASE II. A twenty year old white male was admitted in October, 1951, for episodes of bilateral costovertebral angle pain and the passage of renal calculi. He was well until May, 1951, when he experienced penile pain radiating to the right costovertebral angle. He passed a stone two weeks later, with complete relief of symptoms. The pain recurred two months later, with relief after the passage of a second stone. Gross hematuria accompanied both episodes. The patient gave a history of inflamed, swollen knees at age seven. His other illnesses were varicella, rubeola, pertussis and mumps. Tonsillectomy was performed at age twelve. No other abnormality was detected in frequent routine physical examinations. He has had no bone pain or fractures. Polydipsia, polyuria and nocturia have not been prominent. He habitually drinks 1 to 2 quarts of milk daily.

The patient's father died at forty-five years of tuberculosis and his mother died at fifty-one of hypertensive cerebrovascular disease. He has three sisters and one brother, all reported living and well. The brother has blood chloride and CO_2 content within normal limits and an abdominal x-ray showed no abnormality.

The patient is of short stature but has normal physical findings. When first seen he had a fixed urinary specific gravity, albuminuria, pyuria, azotemia and nephrocalcinosis, as is seen in Figure 5. Skeletal survey, x-rays and cystoscopy were normal.

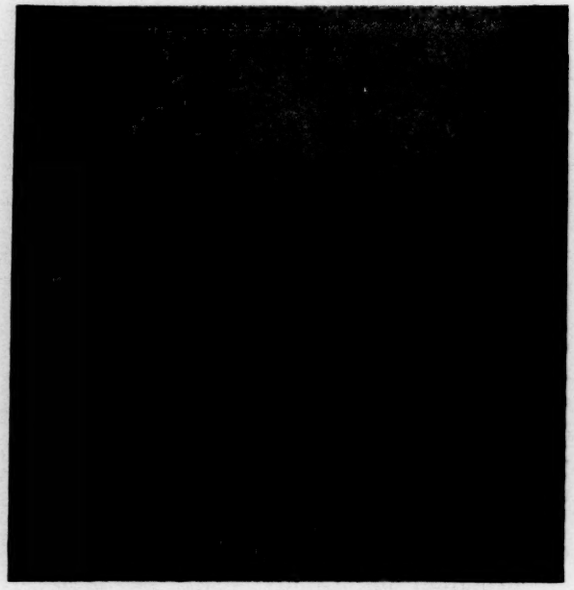

FIG. 5. Case II. X-ray of the abdomen showing elongated kidneys with marked calcium deposition in the renal parenchyma.

In this hospital twenty-two urinary specific gravity determinations ranged from 1.002 to 1.010 with a mean of 1.008. The urine pH ranged from 7.0 to 7.5. Proteinuria has ranged from a trace to 3+. He has had a persistent pyuria and occasional hematuria. Numerous smears, cultures and guinea pig inoculations have been negative for acid-fast bacilli. PSP excretion in June, 1951, was 30 per cent and in October, 1951, 45 per cent in two hours. Urine cultures have been positive for alpha streptococci and Staphylococcus aureus.

Non-protein nitrogen during his second episode of colic was 63 and 82 mg. per cent. It decreased to 38 mg. per cent within a month and has since been about 40 mg. per cent. The blood urea nitrogen has averaged about 22 mg. per cent. Serum calcium determinations have ranged from 8.8 to 13.2 and averaged 11.2 mg. per cent. The serum inorganic phosphorus has ranged from 3.0 to 4.3 and averaged 3.7 mg. per cent. CO_2 combining power has been 17.3, 19.6 and 20.2 mEq./L. The chloride has ranged from 110 to 121 mEq./L. The serum Na was 146 mEq./L. and the K was 4.2 mEq./L. Alkaline phosphatase was 3.9, 6.7, 5.3 and 5.2 Bodansky units.

COMMENTS

Specific renal tubular disorders have recently been receiving more attention.[20] Among the

group may be included renal glycosuria,[21,22] the DeToni-Fanconi syndrome[13,23–27] idiopathic hypercalcuria,[28] pseudohypoparathyroidism,[29] nephrogenic diabetes insipidus,[30] cystinosis[31–33] and the syndrome of renal acidosis which has been described under a complexity of titles. (Table I.) Interest in this disease stems from the complex physiologic alterations accompanying it and the fact that its clinical manifestations may be predominantly in any one of several specialized fields.

Faber and co-workers[10] have presented in tabular form the clinical features of fourteen cases. Pines and Mudge[12] have tabulated an analysis of seventeen cases and excellent reviews have appeared in England.[13,17,19] The probability is great that the disease is much less rare than these numbers indicate. Individual members of the family herein presented have had a known total of twenty-three hospitalizations without recognition of the syndrome, and Pines refers to "six other unpublished instances of this disorder."[12]

It is interesting to note that Williams' studied case of "nephrogenic diabetic insipidus" had a low blood CO_2 and elevated blood chloride concentration. The fact that his cases were familial, and in males, permits speculation on a possible relationship with the syndrome herein described.

Most authors have simply referred to the etiology of this disease as "unknown." Others have postulated "some congenital defect" or specific etiologies such as sulfonamide poisoning[14,38] and pyelonephritis.[9,34] We have found one reference to a case in which the father died of kidney stones,[19] a footnote mentioning calcification in the kidney of a sibling[15] and a report of two siblings ascribed to sulfonamide toxicity.[38] Dent[39] cites this disease as the one renal tubular reabsorption defect which is "never hereditary."

It is believed the present demonstration of the disease in three members (the patient, his brother and son) and a strongly suggestive clinical history in a fourth member (his father) of one family is the first clear indication that the disease can exist on a familial basis. Since the sex incidence in the literature is 4:1 in favor of females, it is of added interest that all affected members in the present report are males.

Very little is known about the pathogenesis of this disorder. Several hypotheses have been advanced. Albright suggested the following sequence: "(1) Inability to make ammonia or to excrete an acid urine due to renal tubular disease; (2) shortage of base with which to excrete mineral acids, notably chloride radicles; (3) increased loss in the urine of calcium acting as a base; (4) tendency to a low serum calcium level; (5) secondary hyperparathyroidism to meet the tendency; (6) hypophosphatemia; (7) "low phosphorus rickets." Peterman has viewed the disease as a consequence of prolonged pyelonephritis. Boyd and Stearns[4] postulated "a perversion of her whole electrolyte system rather than a primary tubular dysfunction." Greenspan[14] has suggested the possibility of chronic carbonic anhydrase poisoning by clinical administration of sulfa drugs. Other authors have claimed that the diabetes insipidus–like state may be responsible for the electrolyte changes. The most fundamental approach has been made by Berliner, Kennedy and Orloff[35] who noted the close correspondence between patients with this disease and animals in which acidification has been impaired either by inhibition of carbonic anhydrase by 6063* or by the administration of maleic acid.[36]

It seems apparent that only two basic mechanisms need be explained in the genesis of this disease: (1) the origin of the hyperchloremia and (2) the inability of the kidney to produce an acid urine in the presence of systemic acidosis. Granting these two defects, the superficially complex manifestations of the disease seem to follow in a logical order. The low ammonia output could be directly related to a limitation in available H ions necessary for conversion of diffusible ammonia to ammonium ion or, perhaps, the high urine pH signifies a failure to challenge the mechanism rather than a primary defect in ammonia production. Indeed, Latner[17] and Milne[13] have both reported a high ammonia coefficient in this disease and in the Fanconi syndrome. The hypokalemia, the neuromuscular disorders and the recurrent tetany may follow the excess loss of K and Ca ions in the urine. Increased Ca excretion and alkaline pH provide the optimum conditions for calcium precipitation in the kidney. The diabetes insipidus–like state is probably a primary end organ deficiency produced by damage to the distal tubular cells by calcium deposits. The bone disease is well considered in the Albright hypothesis as an osteomalacia

* 2-Acetylamino-1,3,4-thiadiazole-5-sulfonamide (American Cyanamid Co.).

secondary to the continued excessive urinary excretion of calcium. This presumably is either simple substitution of calcium as cation or excessive mobilization of calcium from bone consequent to the acidosis. Progressive impairment of renal function can follow the inflammatory and degenerative reaction to calcium deposition[37] and the pyelonephritis so often present and refractory to treatment in the presence of renal calcification. The patients in both cases presented have had severe, prolonged pyuria and several acute urinary infections.

No complete explanation has been offered for the hyperchloremia except to postulate excessive renal reabsorption of chloride or decreased extracellular fluid space as a result of the dehydration. Two explanations have been cited for the other basic mechanism of defective acidification. One theory would emphasize the failure or rate limitation of the hydrogen ion secretory mechanism in the distal tubule. The other stresses failure of bicarbonate reabsorption in the proximal tubule with an apparent inhibition of the acidifying mechanism by the flood of bicarbonate. Further investigation will attempt to distinguish between these possible mechanisms.

It is suggested that this demonstration of a familial pattern should stimulate a careful family survey in every patient in whom the diagnosis of renal acidosis has been made or suspected. It is only by the treatment of early cases so discovered that the true prognosis of the disease will be determined.

SUMMARY

1. A classification of the clinical features of renal acidosis is presented together with a clarification of the terms under which the disease has been described.

2. Two additional patients with the disease are reported.

3. Observations on the family of one patient are offered as the first known demonstration that this disease can exist on a familial basis.

4. Pathogenesis of the disease is discussed.

Acknowledgment: We are pleased to acknowledge the advice of Dr. Robert Clarke and the assistance of Drs. George Heintzelman and Leland Hunter in making the family survey. We are also grateful for the cooperation and interest of the resident and nursing staff of Walter Reed Army Medical Center.

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Hand-Schüller-Christian Disease or Eosinophilic Xanthomatous Granuloma*

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THIS case is reported because of its long duration, widespread involvement and the variety of histologic findings. It occurred in a woman at the time of menopause, which is unusual since Chester and Kugel,[1] in a review of fifty cases found twenty-six below the age of five years and only five in patients older than thirty years. They also found it to be twice as frequent in males as in females.

Up to a few years ago, Hand-Schüller-Christian disease was considered a disturbance of lipid metabolism with excessive storage of cholesterol, to be grouped together with Gaucher's and Nieman-Pick's disease. The first case, described by Hand[2] in 1893, was actually diagnosed as tuberculosis. The literature was well summed up by Rowland[3] in 1928.

Since then opinion concerning the nature of the disorder has changed. Present views on the pathogenesis and classification of Hand-Schüller-Christian disease can be summed up as follows: The basic process is a reticulo-endothelial hyperplasia and granulomatosis, with secondary storage of cholesterol in the histiocytes and final fibrosis and scarring.

As early as 1934 Gerstel[4] called it a generalized granulomatosis. Jaffe and Lichtenstein[5] believe very strongly that Hand-Schüller-Christian disease should be grouped with Letterer-Siwe disease and eosinophilic granuloma of the bone. Some authors go even further and suggest that these three diseases represent different stages of the same basic disturbance.[6–8]

Hand-Schüller-Christian disease does not present hereditary tendencies to match those of Gaucher's and Nieman-Pick's disease, with which it was formerly classified. It has been suggested that instead a different disease reflecting a true cholesterol storage disorder should take its place in that group, namely, familial xanthomatosis or xanthoma tuberosum multiplex.

CASE REPORT

The patient was well up to the age of thirty-seven. Menarche started unusually late and the patient remained childless although married since the age of twenty-five. The menopause came very early, at thirty-seven years, without apparent difficulties and coincided with the first appearance of symptoms typical of diabetes insipidus. In 1944 the patient noticed for the first time a sensitive area in the left parietal region of the skull where presently a bone defect became evident. About that time she also noticed a "stuffy feeling" in her ears and occasional blurred vision. A large node appeared on the left side of her neck. Late in 1946 she started to have occasional convulsive seizures. In 1947, twelve years after the start of her illness, the patient had a thorough check-up at the New England Center Hospital.† Two and one-half years later the patient had to be admitted to the New Jersey State Hospital and from there to the Rhode Island State Hospital because of mental disturbances. She had very weak legs and could not walk. She died in March, 1950, fifteen years after onset of the disease, at the age of fifty-two.

The essential findings on gross examination at autopsy were as follows:

The skull had two round defects filled only by a thin membrane of fibrous tissue (Fig. 1) and two smaller areas of erosion in the left occipital region and right temporal area, which were

† A clinical study of this case by Dr. Siegfried J. Thannhauser is included in his monograph: Lipidoses: Diseases of the Cellular Lipoid Metabolism. The Oxford Medicine, vol. IV, Case XLI, pp. 389–395. New York, 1949. Oxford University Press.

* From the Rhode Island State Hospital for Mental Diseases, Howard, R. I.

FIG. 1. Illustration of skull showing the left fronto-parietal area.

FIG. 2. Photograph of kidney; A, cut surface; B, surface.

visible only on the inner surface and were tightly adherent to the dura. The dura showed extensive areas of thickening, especially over the left parietal area and in the right temporal area, where it was firmly adherent to the brain tissue. In these regions the dura was yellowish and friable, and yellowish nodules were evident also in various locations over the base of the skull. None of these deposits appeared to impinge upon the hypophysis which was of normal size and shape. The brain tissue was yellowish and friable in several areas especially in the right temporal lobe and left occipital lobe corresponding to the dural and bone lesion. Otherwise there were no grossly visible lesions of the brain on section. A chain of markedly enlarged, succulent lymph nodes surrounded the lower abdominal aorta. However, in other locations, particularly in the cervical region where a mass had been described in 1944 (six years previously), no significantly enlarged nodes were found. The spleen was unusually small weighing only 20 gm. and on section appeared dry and fibrotic. The liver was very small weighing 645 gm. but appeared regular in shape. Numerous small, yellowish nodes were present in the capsule and throughout the parenchyma, the largest measuring about 0.7 cm. in diameter. Some nodules had a more reddish-white or hemorrhagic appearance, resembling cancer metastases. The kidneys were small, weighing 75 gm. each. Their surface was distorted by innumerable nodules, slightly raised above the surface, averaging 0.5 cm. in diameter. Here, the lesion was confined to the external surface, the cut surface showed no nodules in the parenchyma. (Fig. 2.)

Sections from the different organs involved illustrate the various stages of Hand-Schüller-Christian disease. Section of the dura, for instance, showed marked fibrous reaction as well as foam cells and lipid storage which showed up very well with Sudan stain. (Fig. 3.) Granulomatous reaction was not evident in these areas. However, sections of nodules in kidney and liver showed more pronounced proliferative and granulomatous features, with many eosinophiles and histiocytes particularly at the periphery whereas the center showed foam cells. (Fig. 4.) Lymph nodes showed the same combination of granulomatous and xanthomatous features, with many large giant cells and numerous foam cells and general reticuloendothelial hyperplasia. (Fig. 5.) The spleen showed extreme thickening of the fibrous framework and atrophy of lymphoid tissue. A section of bone from the second right rib did not include very typical areas. The hypophysis appeared small and the capsule was thickened. Thickened, degenerated dura, as described before, was included in the section but it did not appear to compress or even touch the gland.

A section from the left occipital pole of the brain, representing an area of dural adhesion, showed the same changes as described before in the dura, with foam cells penetrating the brain substance as a direct extension across the pia-arachnoid. A section from the right parietal area, grossly normal, showed extensive foamy vacuolization of the white matter, which showed up as large fat droplets on Sudan stain. The

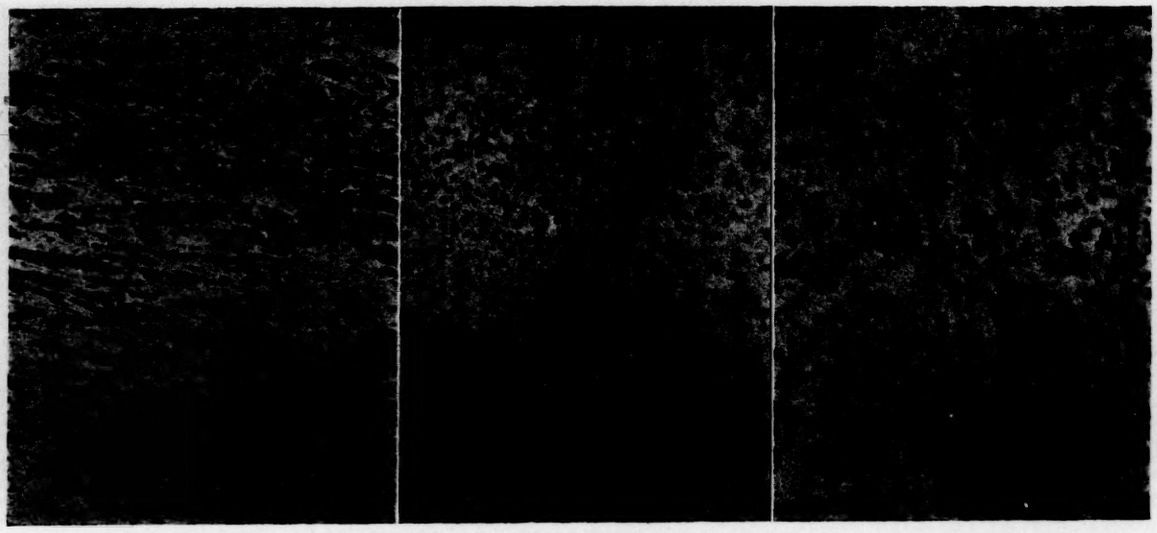

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FIG. 3. Section of dura; Sudan stain × 70.

FIG. 4. Lipogranulomatous nodule in liver; hematoxylin and eosin stain × 301.

FIG. 5. Lymph node; hematoxylin and eosin stain × 301.

cortex here appeared fairly normal, with no lipid deposits in the neurons. Some chromatolysis was evident. First layer gliosis was present due to proliferation of astrocytes in the cortex. A section from the tuber cinereum and hypothalamus stained by the Nissl method (courtesy of Dr. H. Williams, R. I. Hospital) showed no unusual features.

COMMENT

This is, then, a woman with Hand-Schüller-Christian disease followed for fifteen years, between the ages of thirty-seven and fifty-two. It had affected lymph nodes, bone, dura, brain, liver and kidneys. No causative factor could be found but the unusual menstrual history may suggest some endocrine dysfunction.

The absence of demonstable lesions of the hypophysis, tuber cinereum and hypothalamus leaves us without an explanation for the long history of diabetes insipidus. There is, however, the possibility that an early lesion was present near the hypothalamus or stalk of the hypophysis which had since become fibrosed and healed. One of the brain sections clearly demonstrated that the lipogranulomatous lesion could involve brain tissue. We also can assume that the large lymph node, which had been described six years before, had since undergone healing and atrophy and that the extremely small, fibrotic spleen represents the end-stage of a previous lipogranulomatous involvement.

The contrast between the histologic appearance of the lesions in the dura, which we know to be more than six years old (time of appearance of bone lesions) and the nodules in liver and kidney, which were clinically unsuspected and small in size, suggests that lesions appear in successive crops, starting as granulomatous proliferation, with subsequent cholesterol storage in the histiocytes and proceeding to fibrosis and ultimate disappearance. Some of the nodules in liver and kidney bore a striking resemblance to eosinophilic granuloma as described by Jaffe and Lichtenstein.[5] In Schafer's[9] report of three cases of Letterer-Siwe disease, one can find a photomicrograph of thymus which is very similar to one of our lymph nodes. (Fig. 5.) This case, therefore, represents a good illustration of the similarities between Letterer-Siwe disease, eosinophilic granuloma of bone and Hand-Schüller-Christian disease.

SUMMARY

A case of Hand-Schüller-Christian disease is presented with detailed description of lesions found at necropsy. Some of the theories concerning pathogenesis are briefly discussed.

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Auricular Sounds in a Case of Auricular Flutter*

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While the criteria reiterated by Levine and Harvey[1] may occasionally lead one to suspect the existence of auricular flutter, the diagnosis of the condition usually is made by the electrocardiographer. We recently have had the experience of hearing rather loud, regular and rapid precordial clicking sounds in a patient with complete heart block in whom the diagnosis of auricular flutter seemed obvious before the electrocardiogram was taken.

Precordial clicking sounds occurring synchronously with the waves of auricular flutter in the electrocardiogram have previously been described[1–9] in varying detail since 1931 when the subject was first reported by Bennett and Kerr.[2] The present case is unique in that the flutter sounds are still present almost a year after they were first detected.

CASE REPORT

T. J., a forty-one year old Negro housewife, was admitted to the Cincinnati General Hospital on June 5, 1950, because of uterine bleeding.

For six months she had had irregular profuse uterine bleeding which during the last three months was accompanied by progressive weakness, exertional dyspnea, orthopnea and slight dependent edema.

Past history revealed that she had always been slight of build and easily fatigued. For as long as she could recall she had been unable to deviate her eyes in any direction and had had severe ptosis of both eyelids.

Physical examination on admission revealed a normal temperature, pulse 72, respirations 18, blood pressure 200/110. There was severe ptosis and complete external ophthalmoplegia. The pupils were unequal in size and reacted sluggishly to light. Retinal vessels showed grade 1 changes. The neck veins were engorged; there were basal pulmonic rales. The heart was enlarged to the left, with many premature ventricular contractions, at times producing pulsus bigemini or trigemini. There was a loud-blowing apical systolic murmur. The liver edge was palpable at the costal margin. Uterine fibroid tumors could be palpated on pelvic examination. Mild dependent edema was present.

Laboratory work revealed the hemoglobin to be 7 gm., with normal white blood count and differential. Urinalysis failed to disclose any abnormality. Cardiac fluoroscopy and roentgenograms of the chest revealed left ventricular enlargement and dilatation of the left auricle, producing a double contour along the right cardiac border. Congestive changes were present in the lungs. Electrocardiogram revealed third degree heart block with premature ventricular contractions originating from numerous foci and prolonged electrical systole. The auricular rate was 61, the ventricular rate 60.

On a non-specific regimen blood pressure fell to 140/80, and the extrasystoles decreased in frequency. The patient was given transfusions of whole blood, bringing the hemoglobin level to 10 gm. Hysterectomy was performed on September 18, 1950. Subsequently her general condition remained good and all signs of congestive failure disappeared. The cardiac silhouette became smaller, the murmur decreased in intensity and she gained weight. The heart rate varied from 36 to 48 per minute. Because of continued weakness ephedrine was begun on March 2, 1951, ultimately in doses of 75 mg. daily, with amytal 150 mg. daily. Subjective improvement was marked. From time to time slow precordial clicks were noted which were interpreted as normal auricular contractions.

On December 27, 1951, a ventricular rate of 36 was found. A rapid regular clicking sound

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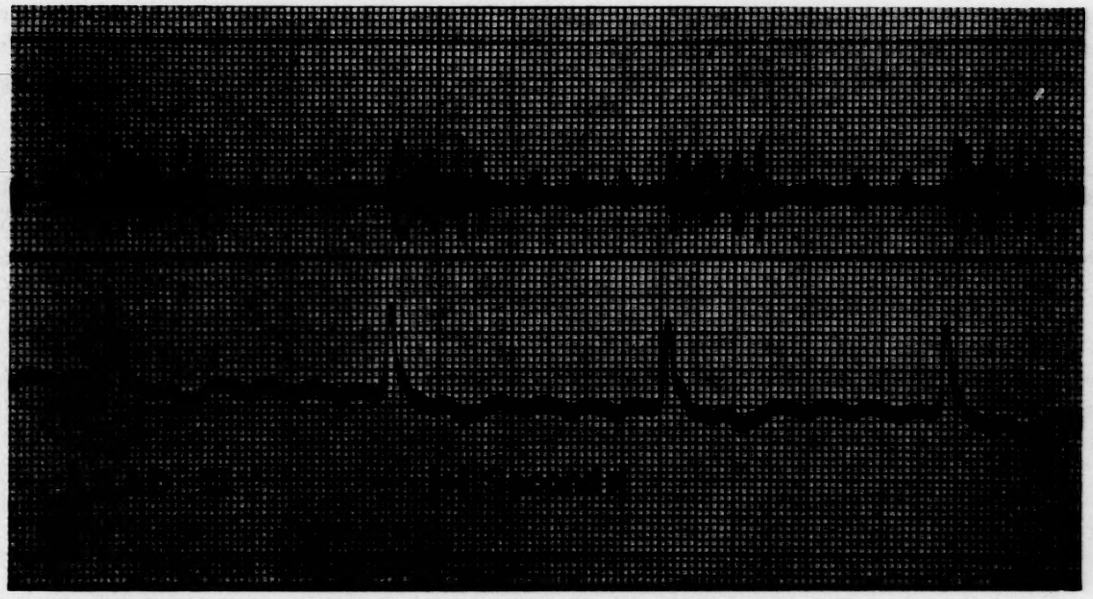

FIG. 1. Simultaneous phonocardiogram and electrocardiogram, showing graphically the flutter sound. The phonocardiogram was taken in the third intercostal space 6 cm. lateral to the mid-sternal line.

was also clearly audible over most of the left side of the precordium but best over the third rib 6 cm. to the left of the mid-sternum. An electrocardiogram revealed auricular flutter, with slow dissociated ventricular rhythm. The rate of the flutter roughly corresponded to that of the adventitious sound.

Simultaneous electrocardiogram and phonocardiogram taken January 3, 1952, revealed synchrony between the flutter and the previously described sounds. The rate of both was 230 per minute, and the ventricular rate was 45 per minute. (Fig. 1.) The transverse diameter of the heart appeared to be greater than previously. Cardiac fluoroscopy on January 3, 1952, revealed that pulsations of the heart were normal in intensity but quite slow, and no evidence of flutter of the auricular regions or of the adjacent esophagus was demonstrated. The left ventricle was enlarged in the frontal and left oblique views; the left auricle showed a definite enlargement as seen through the heart in the view postero-anterior, and posterior bulging in the right oblique. This has increased since the previous examination one and a half years ago. No other chamber enlargement was seen. No abnormal hilar pulsations or intracardiac calcifications were noted. Diaphragmatic flutter was not present.

This phenomenon has persisted to the present. The clicks have been heard best in the supine position, less well in either lateral decubitus position. They decrease markedly when the patient sits up. There is an inconstant irregular variation in intensity of the clicks, which is related neither to respiration nor position within the cardiac cycle. The patient has remained essentially asymptomatic.

On November 3, 1952, an electrocardiogram showed no change from previously except that the ventricular rate was then 52. The auricular flutter was as before. Ballistocardiogram was made in an attempt to demonstrate a ballistic impulse in the auricles but failed to reveal more than non-specific changes.

COMMENTS

The nature of the heart lesion in this case is undetermined, although a congenital basis for the heart block has been suggested. The coexistence of what appears to be a congenital lesion of the oculomotor apparatus gives this thesis support.

The association of complete heart block with auricular flutter is considered to be rare, although Hanssen[10] noted flutter in seven of sixty-six consecutive cases of complete heart block. However, of the reported cases of audible flutter waves most have been described in patients with associated heart block.[1,3–6,9] It is possible that the prolonged diastolic silence merely allows keener perception of the auricular tones. In fact the normal auricular tones are occasionally heard in complete heart block,

perhaps for this same reason. However, the intensity of the auricular sounds in this case was great enough to permit easy detection even if the ventricular rate were faster, and this doubtless held true in at least one of the other reported cases.[8] It is suggested that the combination of complete heart block and flutter may predispose to greater audibility of the flutter contractions.

SUMMARY

A case is reported of complete heart block in a woman of forty-one in whom the diagnosis subsequently of auricular flutter was made on the basis of rapid precordial clicks. The clicks have persisted for almost a year, the patient meanwhile remaining essentially asymptomatic.

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Fatal Bone Marrow Embolism Occluding the Pulmonary Arteries*

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EMBOLISM of pulmonary arteries by bone marrow particles is rare. With few exceptions, in most of the reported cases the finding was an incidental one and of minor degree or significance. The following case report is therefore considered worth while since bone marrow embolization occurred in an unusual manner, was rapid, massive and resulted in sudden death.

CASE REPORT

J. H. was a fifty-nine year old white male who developed tuberculous spondylitis in 1922. Shortly thereafter he developed paraplegia which had kept him confined to bed for the past thirty years. He was hospitalized in 1947 for active pulmonary tuberculosis but the process was believed to be quiescent at the time of discharge several months later. His present admission to Minneapolis Veterans Administration Hospital occurred on April 9, 1952, because of a marked weakness and shortness of breath three days before admission. Physical findings on admission revealed blood pressure of 112/80 mm. Hg; temperature 98.6°F.; pulse 80/minute. Dulness was present over the left lower chest and occasional crackling rales were present over both lower lung fields posteriorly. The legs were ankylosed in the position of full extension. Complete anesthesia below the umbilicus was found and the patient was incontinent of urine and feces. Reflexes were normal in the upper extremities.

Laboratory findings included hemoglobin of 12.4 gm. per cent; white blood cells 29,000/cu.mm. with 92 per cent neutrophils and 8 per cent lymphocytes; erythrocyte sedimentation rate 4 mm./hour. Three plus albumin was present in the urine and the urine was "loaded" with white blood cells and red blood cells. The blood urea nitrogen was 21 mg. per cent. Urine culture revealed growth of Proteus sp. and inoculation of a guinea pig was reported after death as revealing virulent tubercle bacilli. A chest roentgenogram revealed a shift of the mediastinum to the left and thickened pleura over the entire left lung and the right base. Scattered calcification was noted through the right lung and mottled calcification about the lower dorsal vertebrae. It was believed the patient had a pyogenic urinary infection and on May 9, 1952, an attempt was made to evaluate the extent of this process. An intravenous pyelogram was unsatisfactory. The patient was placed on his back on the cystoscopy table for a retrograde pyelographic study. Because of the ankylosis of the legs in full extension, considerable difficulty was encountered in placing the patient in the proper position. This was finally accomplished when a physician grasped the patient's ankles, vigorously raised and abducted the legs. At that time the urologist placed 20 cc. of 1/400 nupercaine solution into the urethra as a local anesthetic. Within thirty seconds the patient became deeply cyanotic and respiration ceased very quickly. As soon as the cyanosis was observed the nupercaine was withdrawn from the urethra and 1½ gr. of sodium luminal given intravenously as well as 3 minims of adrenaline subcutaneously. The pulse was still palpable after respiration ceased. The trachea was intubated and oxygen was given and this resulted in some improvement of color. The latter, however, was very transient and cyanosis again ensued after which the heart and pulse were no longer palpable. The chest was entered and cardiac massage resulted in feeble spontaneous cardiac contractions which

* From the Department of Pathology, Veterans Administration Hospital and University of Minnesota Medical School, Minneapolis, Minn. Published with the approval of the Chief Medical Director of the Veterans Administration. The statements and conclusions published by the authors do not necessarily reflect the opinion or policy of the Veterans Administration.

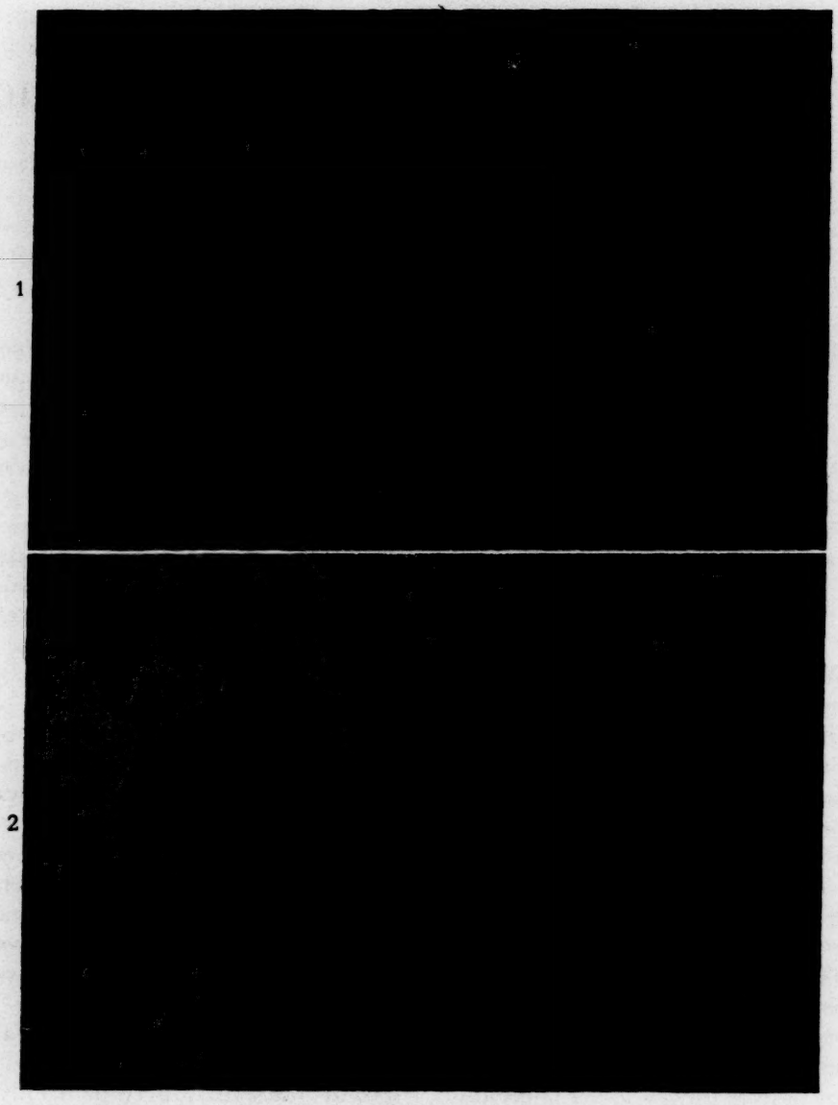

FIG. 1. Lung; the lumina of several pulmonary arteries are occluded by bone marrow particles; hematoxylin and eosin stain, × 46.

FIG. 2. High power view of several arteries shown in Figure 1; hematoxylin and eosin stain, × 155.

lasted fifteen minutes and kept the blood pressure at about 80 mm. Hg systolic. Permanent cardiac arrest then occurred. Although no convulsions had occurred at any time, the clinical diagnosis was hypersensitivity reaction due to nupercaine.

At necropsy the heart and coronary tree revealed no gross pathologic condition. The right lung weighed 500 gm. and was moderately edematous. Scattered calcifications up to 3 mm. in diameter were found in all of the lobes. The left lung was completely atelectatic and covered by greatly thickened pleura which contained some colorless gelatinous areas. The pulmonary vascular tree was carefully dissected without finding any gross evidence of obstruction. The kidneys appeared grossly normal except for multiple calculi in the calices and pelvis on both sides. An abscess containing 20 cc. of creamy pus was found in the prostate. A caseous nodule 1 cm. in diameter was found in the right testis. Examination of the spine revealed that the fourth, fifth and sixth thoracic vertebrae were extensively replaced by an amorphous white material with the consistency of a thick gritty paste. Cultures and guinea pig

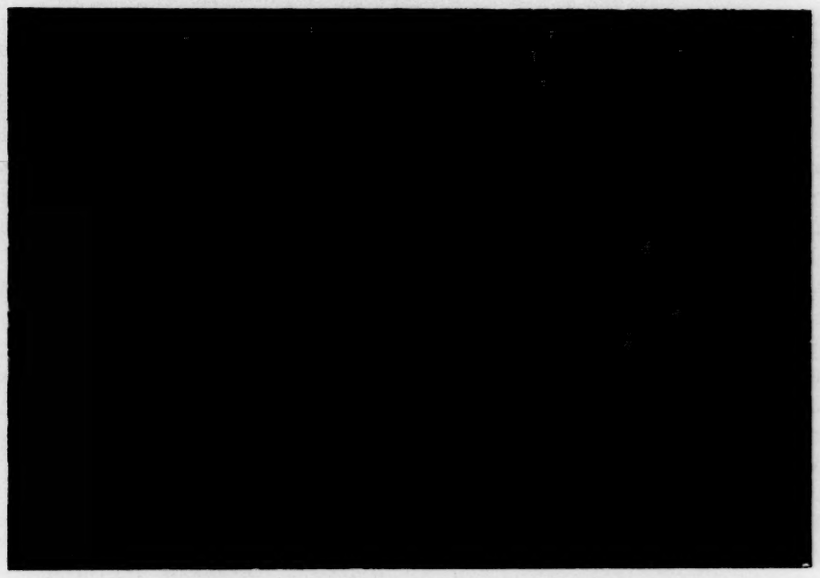

FIG. 3. Section of bone marrow of diseased vertebra. The edge of a large caseous area is seen replacing bone marrow; hematoxylin and eosin stain, × 46.

inoculations of material from the pleura, prostate and testis all yielded virulent tubercle bacilli. These studies were negative on the material from the spine but histologic sections described below showed clearly that the process was also tuberculous and that some residual activity remained even though acid-fast bacilli were not demonstrated in vertebral material.

Microscopic examination revealed active caseous tuberculosis of the testis, prostate and pleura. Sections of the lungs revealed embolization of the pulmonary arteries by bone marrow fragments. (Figs. 1 and 2.) Approximately thirty sections from many segments of all lobes were examined and revealed a uniform picture. Vessels ranging in size from 20 up to 500 micra in diameter were completely occluded by hematopoietic tissue. Fat stains revealed the presence of neutral fat in a few of the interalveolar capillaries. Acid-fast stains showed no acid-fast bacilli in the arteries. Bone fragments were not found. The degree of embolization was massive. No fat or marrow could be found in the kidneys or brain. Large areas of caseous necrosis were present in the grossly involved vertebrae with an active peripheral zone made up of lymphocytes, epithelioid cells and multinucleated giant cells in some areas. (Fig. 3.) A mild degree of amyloidosis was found in the renal glomeruli and spleen.

In retrospect it was believed that compression of the diseased vertebrae had occurred consequent to vigorous manipulation at cystoscopy, allowing vertebral marrow to enter the circulation.

COMMENTS

Bone marrow embolism is an unusual phenomenon usually following fractures of bones containing red marrow. After Lubarsch's initial observation of this condition in man in 1897 and its experimental reproduction in rabbits,[1] the literature contains little mention of it until the past few years. In a review of fat embolism in 1946 Warren[2] mentioned three cases which had associated bone marrow embolism, and Lindsay and Moon[3] reported three cases of multiple fractures whose lungs contained an occasional embolus composed of bone marrow; one of the three also had a rather extensive pulmonary fat embolism. In 1951 Berkheiser and Giffen[4] reported a case of fat embolism with an occasional bone marrow embolus in an eighty-two year old white male two hours following the reduction of a fractured radius. That same year Fisher[5] reviewed routine lung sections of ninety-six cases of fractures and found nineteen that contained an occasional artery embolized by bone marrow. He emphasized that such emboli "were never numerous." Schenken and Coleman[6] reported one case of bone marrow embolism associated with extensive fat embolism after operative reduction of a fracture of the neck of the femur.

Bone marrow emboli have been found in vessels ranging in size from interalveolar capillaries to pulmonary arteries as large as 520 micra. Most of the emboli apparently lodged within 3 cm. of the pleural surface; they appeared to cause very little reaction in the wall of the vessels in which they were found. They consisted of hematopoietic tissue embedded in adipose tissue, identical in appearance to that found in red bone marrow. Bone fragments and even small arterioles have been found in such emboli. Rappaport et al.[7] stated the presence of bone marrow fragments may have medicolegal significance, implying bone fracture even if none was found at autopsy.

The time interval between injury and death in cases showing bone marrow embolism has varied from a few minutes to six days. Fisher[5] called attention to the rapidity with which embolization may occur, citing several cases in which death was almost instantaneous yet an occasional marrow embolus was found. Many of the reported cases were traumatic with fractures of bone containing red marrow. Most of those without demonstrable fracture suffered from convulsions prior to death. In these cases severe trauma to (if not actual fracture of) the vertebra may be hypothesized.

An excellent review by Rappaport et al.[7] added twenty-seven cases; two of the twenty-seven cases had massive embolism. These are of particular interest since in all previously reported cases the bone marrow emboli were either so few in number that they had to be considered as purely accidental findings or were certainly of secondary importance with respect to the extent of the fat embolism with which they were frequently associated. These are the only reported cases with which we are familiar in which pulmonary embolism by bone marrow was clearly so massive as to be considered the immediate cause of death.

Patients with vertebral tuberculosis commonly are subjected to cystoscopy to investigate the kidneys which are often a coexistent infected site. This case demonstrates the hazard of forcibly flexing the spine during the procedure, particularly if the lower dorsal or lumbar vertebrae are involved. The importance of examining every case of sudden death thoroughly is emphasized when one considers that the cause of death would have been ascribed to the anesthetic if a careful autopsy had not been performed.

SUMMARY

A case of sudden death due to massive bone marrow embolism is reported. The marrow apparently entered the circulation consequent to inadvertent compression of tuberculous vertebrae during cystoscopy.

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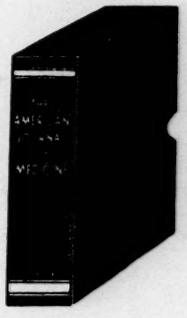

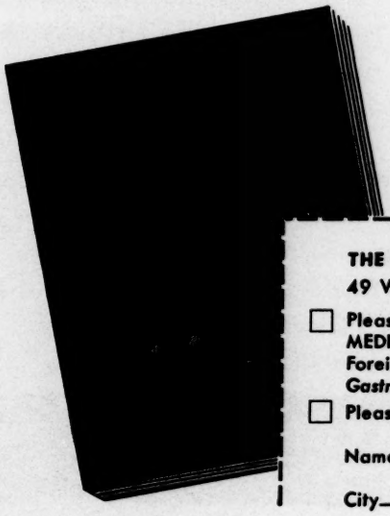

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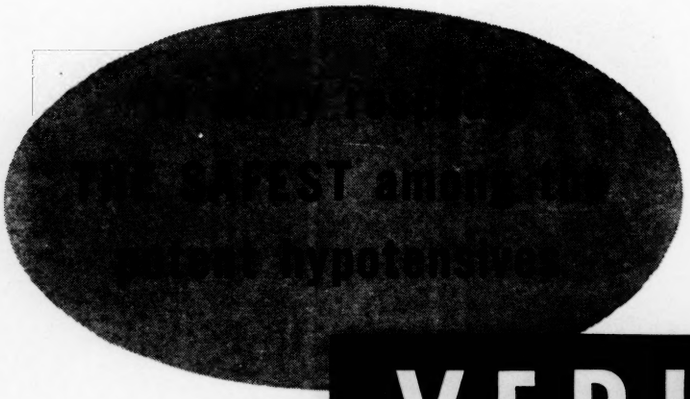

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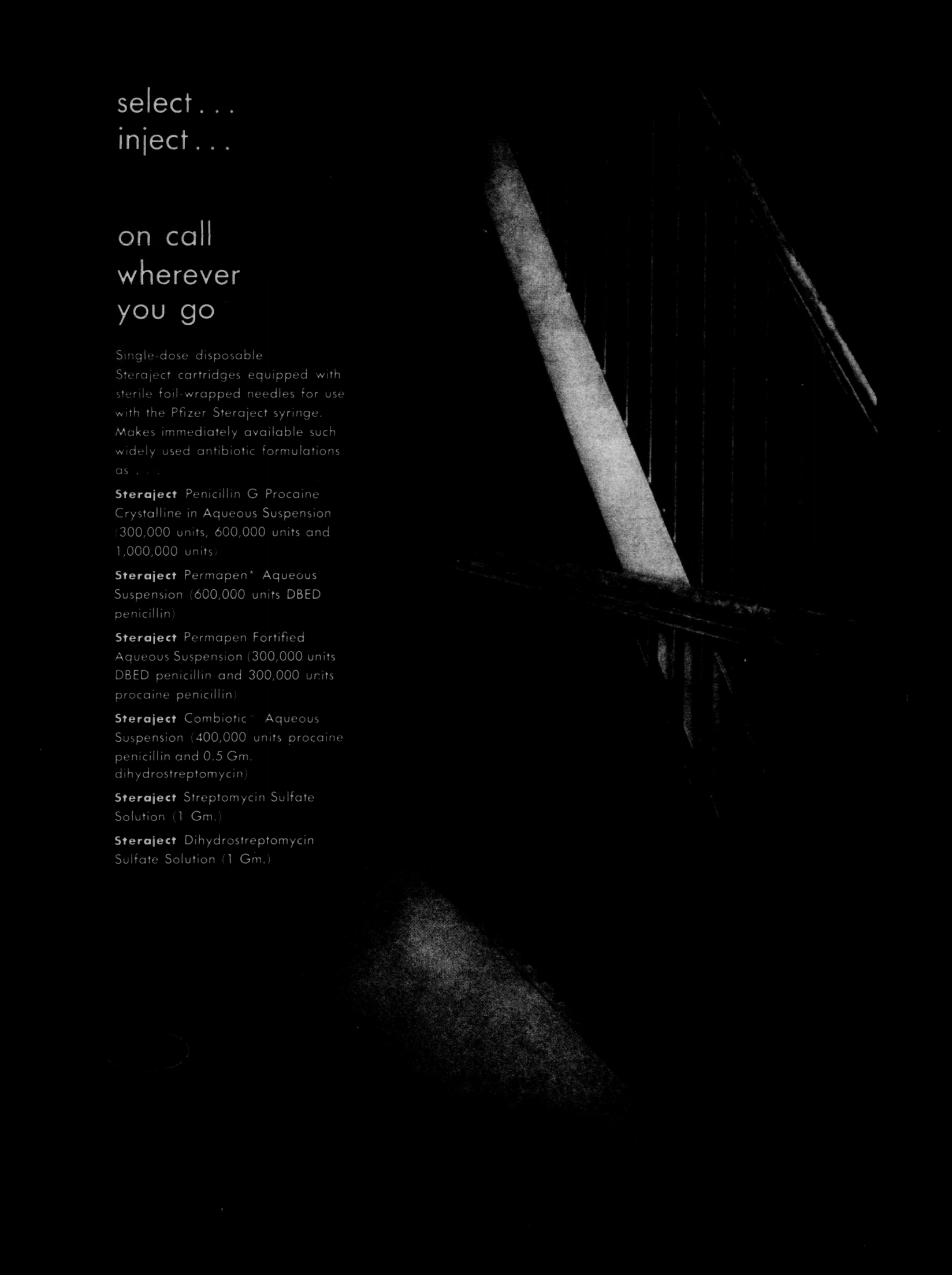

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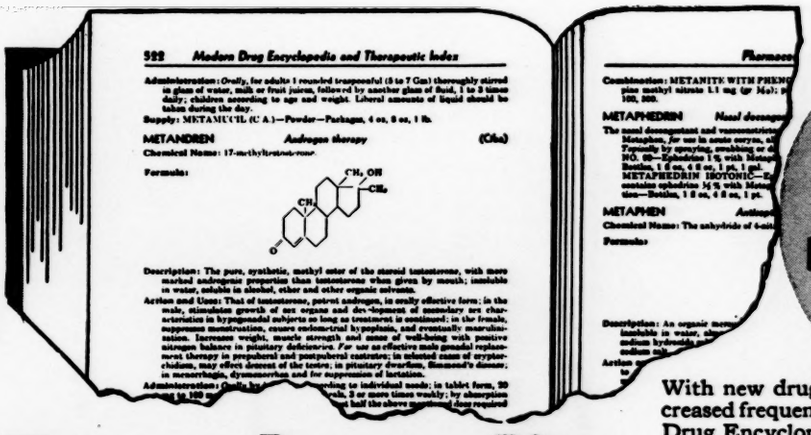
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Pharmacol
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METAPHEN
Chemical Name: The anhydride of 6-nitro
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Encyclopedia INDEX

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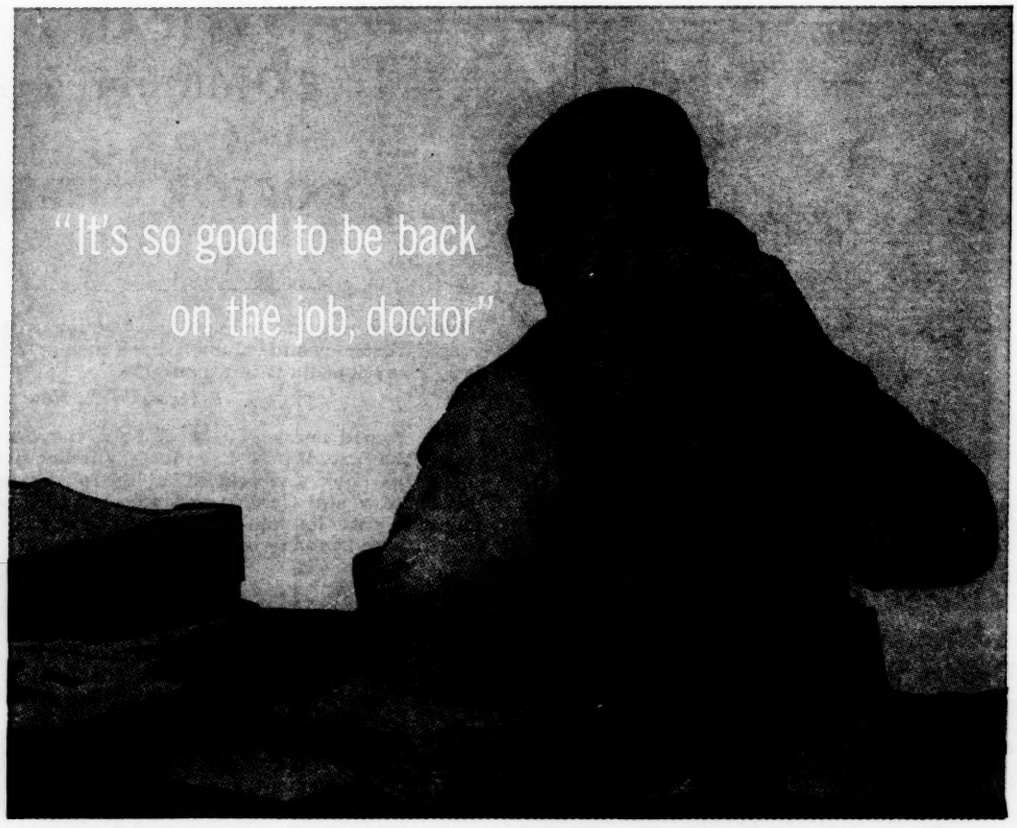

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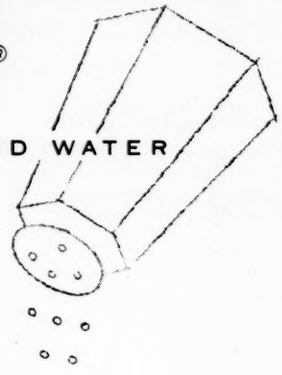

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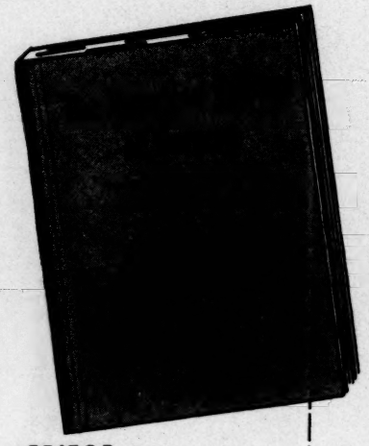

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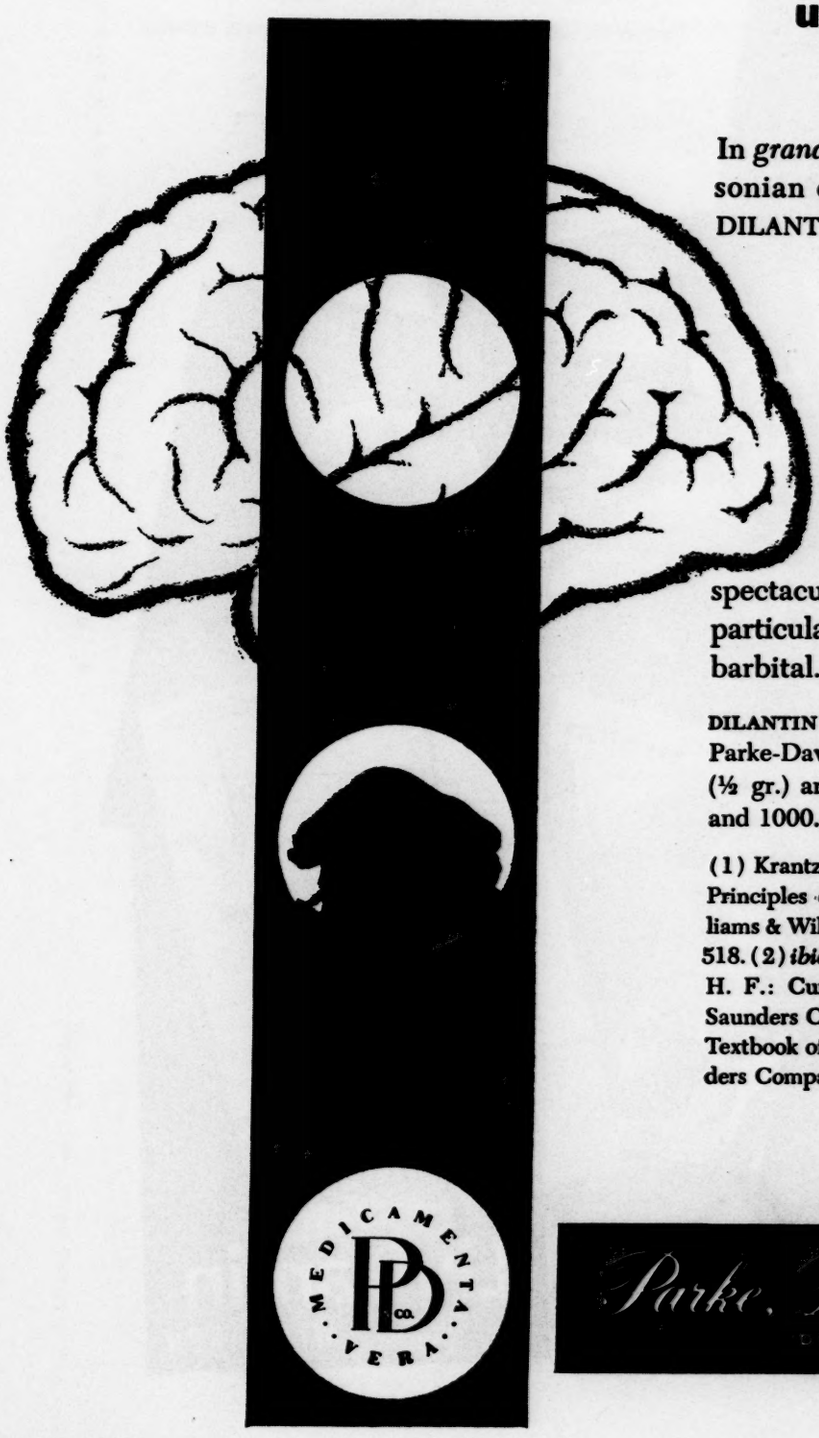

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(1) Krantz, J. C., and Carr, C. J.: The Pharmacologic Principles of Medical Practice, Baltimore, The Williams & Wilkins Company, 1949 (Reprinted 1950), p. 518. (2) *ibid*, p. 515. (3) Carter, S.: Epilepsy, in Conn, H. F.: Current Therapy 1952, Philadelphia, W. B. Saunders Company, 1952, p. 612. (4) Salter, W. T.: A Textbook of Pharmacology, Philadelphia, W. B. Saunders Company, 1952, p. 231.

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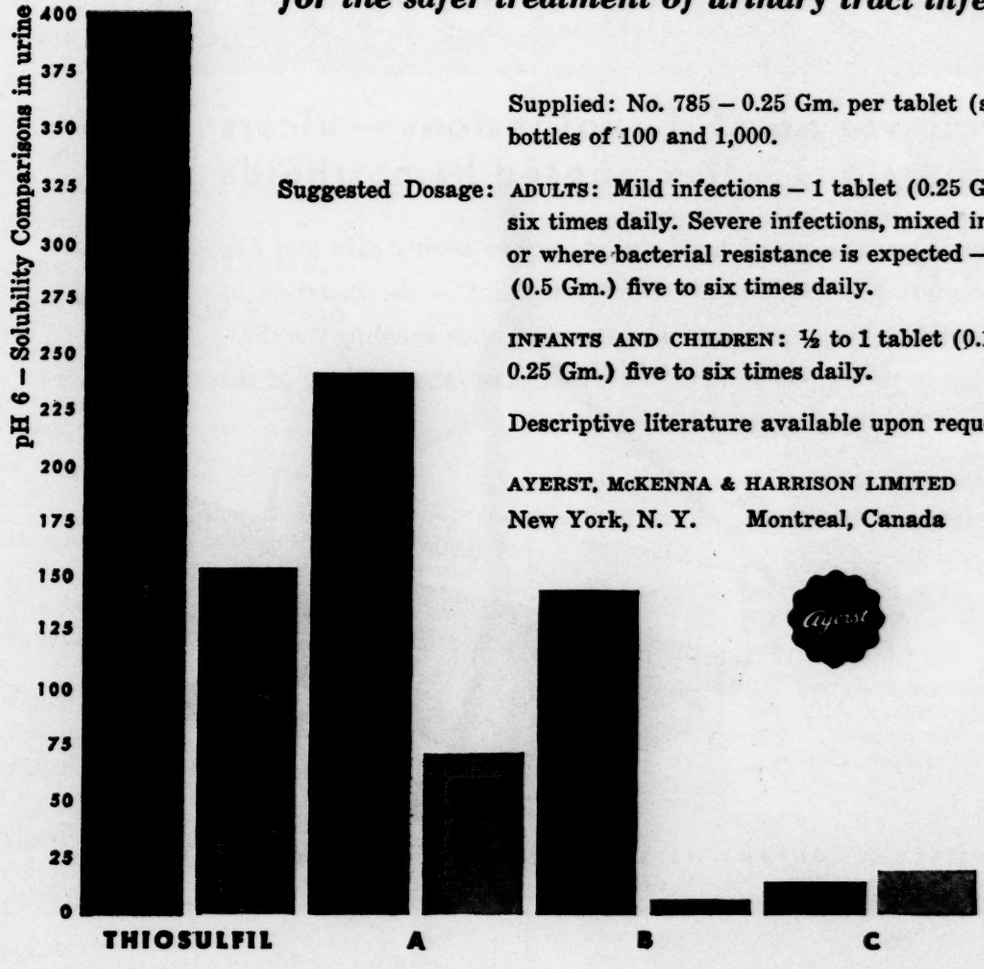

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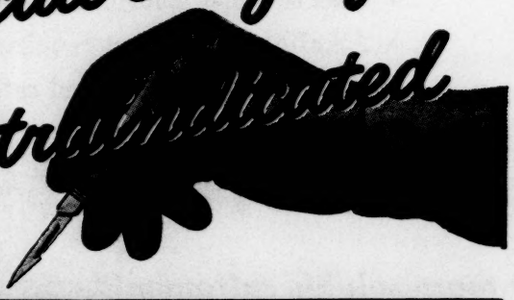

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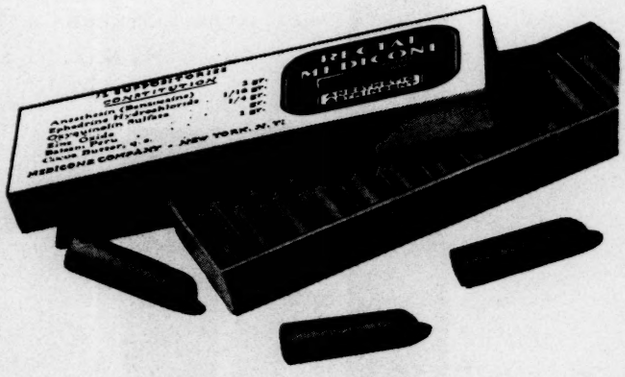

[1]*Bargen, J. A., and Jackman, R. J., Journal Lancet, 72:11, Nov., 1952.*

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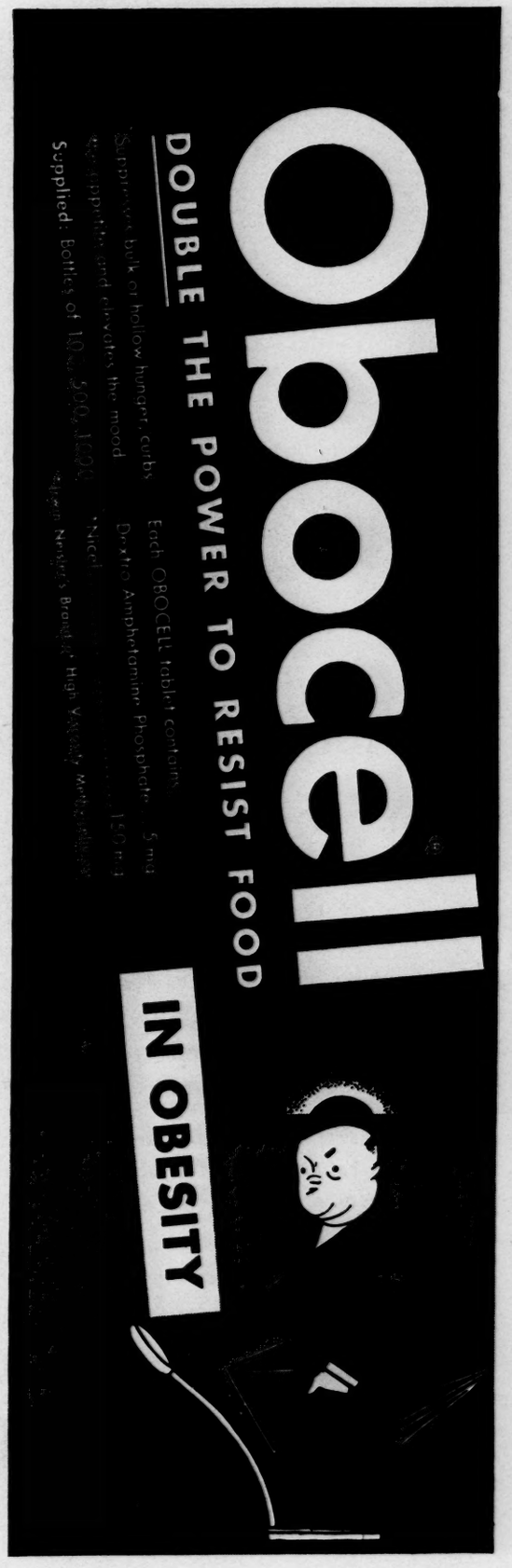

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